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THE EFFECT OF SENSITIVITY ON THE DISTRIBUTION OF TUBERCLE BACILLI IN TUBERCULOSIS[1,2]

WILLIAM L. BROSIUS AND C. EUGENE WOODRUFF

A careful study of tuberculous patients with regard to their sensitivity to tuberculoprotein has revealed that, in many cases, as the patient reaches the terminal stages of his infection he fails to react to the usual intracutaneous doses of tuberculin (1). In this study some of the patients were found to be anergic to even 10 mg. of tuberculin. Four of the latter came to autopsy. Histological examination of their tissues showed in each case a type of cell reaction and of tissue damage different from that ordinarily observed in tuberculosis although the lesions were teeming with acid-fast bacilli. The suggestion was made that this atypical appearance of tuberculosis might be the result of the anergic condition of the patient. This explanation seemed the more likely when experimental studies on tuberculous guinea pigs (2, 3) revealed that animals losing their capacity for allergic reaction developed noncaseous pulmonary lesions which were filled with acid-fast bacilli, while the animals highly sensitized at the time of death showed few or no acid-fast bacilli in their lungs.

In an attempt to clarify the question of the relation between skin sensitivity and the type of lesion in human tuberculosis, a study has been made of autopsy material from 29 tuberculous patients whose sensitivity level shortly before death was known.

MATERIAL AND METHODS OF STUDY

The material for study came from patients who died on the Tuberculosis Service of two of Detroit's Municipal Hospitals. It is the custom in one of these institutions to give an intracutaneous tuberculin test to each patient on admission, the initial test consisting of 0.1 cc. of 1:10,000 OT (0.01 mg.). The tests are read at the end of forty-eight hours, an area of induration 5 mm. or more in diameter being considered a positive test. Patients negative to the first dilution are retested at forty-eight-hour intervals with tuberculin 10 times as concentrated, the final dilution used being 1:10 OT (10 mg.). Following these admission tests, when patients' names appeared on the critical list, they were similarly tested. Since the sensitivity level of both animals and man, as indicated by skin reaction, may change fairly rapidly, it was necessary to exclude all of those cases in which the interval between tuberculin test and death was too great. This time interval was set arbitrarily at ten days. Twenty-nine autopsied cases, on which a tuberculin test was performed within ten days of exitus, form the basis of the data appearing in table 1.

At some of the autopsies, the lungs with the trachea were removed intact,

[1] From the Herman Kiefer Hospital, Detroit, and the Wm. H. Maybury Sanatorium, Northville, Michigan.

[2] Presented before the Medical Section at the 40th annual meeting of the National Tuberculosis Association, Chicago, Illinois, May 10, 1944.

inflated to antemortem volume and roentgenographed. The postmortem roentgenograms were compared with the series of roentgenograms made before death to determine, where possible, the relative ages of the lesions.

The autopsy material was fixed in 10 per cent formalin. Histological sections from the lungs were stained with haematoxylin and eosin and by the Ziehl-Neelsen method, using Loeffler's methylene blue as a counterstain. The sections stained to show acid-fast bacteria were examined carefully for tubercle bacilli. In some instances the bacilli were so numerous that they could be identified as red-staining masses under the low power objective. If 5 or more bacilli could be identified per oil immersion field, the slide was recorded as having "numerous" bacilli. "Few" bacilli were recorded when less than 5 bacilli were found per immersion field, usually only one or two bacilli were found on the entire slide. The recording of *no* bacilli was made after examining a given slide for at least four minutes.

TABLE 1

*Skin sensitivity as related to the number of acid-fast bacilli in the lungs of tuberculous patients**

NUMBER OF CASES	SKIN SENSITIVITY LEVEL	PRESENCE OR ABSENCE OF TUBERCLE BACILLI		
		0	Few	Numerous
		Number of cases		
3	Positive to 0.01 mg. (1:10,000 OT)	3	0	0
8	Positive to 0.1 mg. (1:1000 OT)	7	1	0
5	Positive to 1.0 mg. (1:100 OT)	2	3	0
2	Positive to 10.0 mg. (1:10 OT)	0	2	0
11	Negative to 10.0 mg. OT or more	0	0	11

* Cavities lined with necrotic material and with a fibrous wall are excluded from the tabulation because, as explained in the text, the bacilli in them are exteriorized from the inhibiting factors of sensitivity.

PATHOLOGICAL FINDINGS

Data from the 29 autopsies are summarized in table 1. The last group in table 1 includes those cases which failed to react to 10 mg. of OT. It will be noted that the cases in the groups which had the higher levels of skin sensitivity showed few or no acid-fast bacilli in their lesions, while in *all* of the 11 cases at the lowest sensitivity level the lesions contained numerous bacilli.

Even more important than the difference in number of bacilli was the marked difference in character of the lesions. In patients who reacted to 1:1000 or 1:10,000 OT shortly before death the few bacilli which were found were in completely caseous tissues or exudate (figure 1). In the cases with little or no sensitivity, bacilli were found in great numbers, often in a frankly pneumonic process where the alveoli, with walls intact, were filled with polymorphonuclear leucocytes, large mononuclear and epithelioid cells and where the bacilli appeared to be proliferating in or on these living cells (figures 2 and 3).

Frequently in patients who had lost their sensitivity, caseous lesions com-

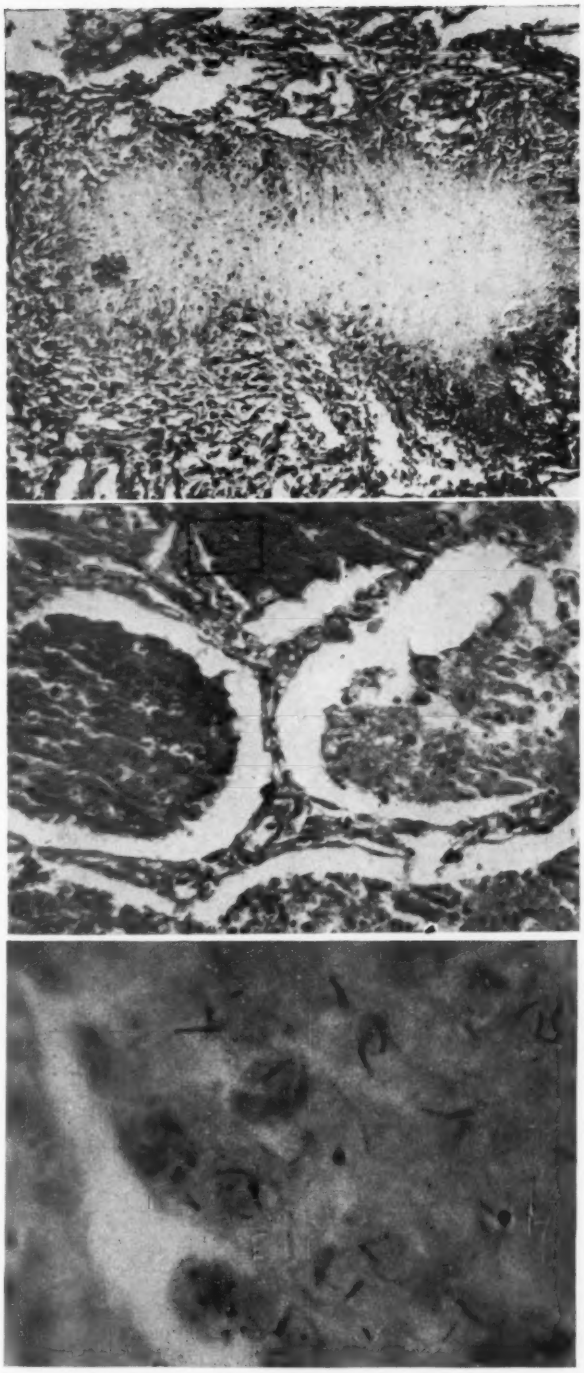
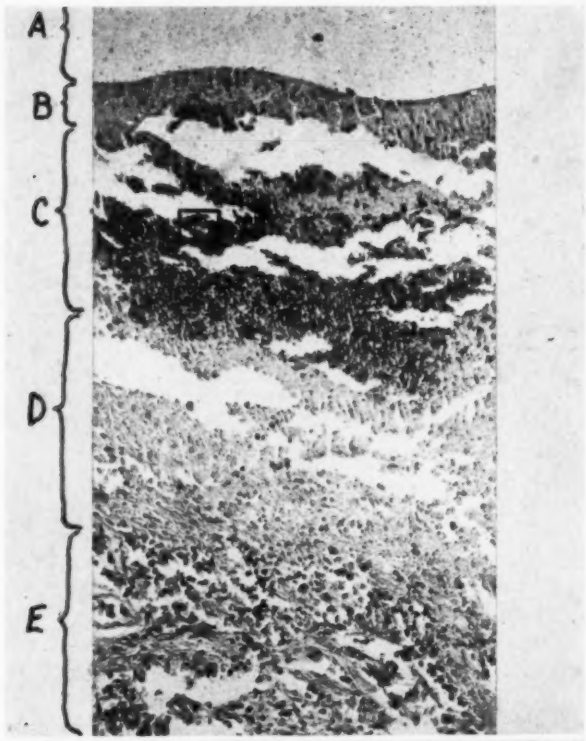


FIG. 1. (Top) Tubercle in the lungs of a patient who had a high level of sensitivity at the time of death. The central caseation is characteristic. A single tubercle bacillus found in the caseous centre was the only acid-fast bacillus demonstrable. × 150.

FIG. 2. (Centre) Tuberculous lesion from anergic patient who, a few days before death, failed to react to 10 mg. of OT. Note that the alveolar walls are intact though the exudate within the alveoli is teeming with tubercle bacilli. In the highly sensitized patient tubercle bacilli are never found in contact with living tissues. × 200.

FIG. 3. (Bottom) Higher magnification of area outlined in figure 2 to show the great numbers of acid-fast bacilli. × 1500.



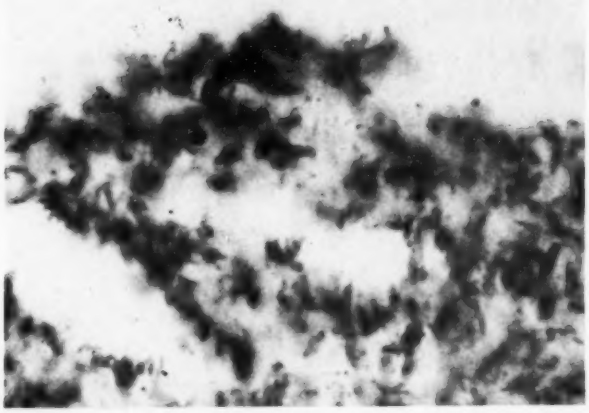


FIG. 4. (Top) Tuberculous cavity. (A) Lumen of cavity. (B) Superficial layer of exudate. (C) The dark areas are solid masses of tubercle bacilli. (D) Layer of necrotic exudate. (E) Pulmonary tissues which were apparently living when the patient died. There are no acid-fast bacilli in these living tissues. × 150.

FIG. 5. (Bottom) Higher magnification of area outlined in figure 4 showing the great masses of tubercle bacilli which have grown in the exudate of the cavity as they might in culture media. × 1500.

pletely devoid of acid-fast bacilli were found side by side with lesions teeming with bacilli. Invariably a considerable difference in the age of such lesions was noted. The bacillus-free lesions always appeared to be many weeks old, as indicated by encapsulated caseation or fibrosis. The bacillus-rich lesions, in contrast, were of relatively recent origin, being exudative in type without encapsulation. While foci of noncaseous necrosis were found, most of the tissue and exudate was composed of cells which apparently were living at the time of death of the patient. In patients with high levels of sensitivity, lesions were studied which serial roentgenograms showed to be recent disseminations and which presented, microscopically, the criteria usually accepted as indicative of short duration. Such lesions were almost completely devoid of bacilli.

Tuberculous cavities were studied with especial care. In tissues from patients with high levels of sensitivity sections through the walls of some of the cavities showed tubercle bacilli in large numbers in the semifluid, partly necrotic exudate lining the cavity wall (figures 4 and 5). Where bacilli were found in such material there was always a layer of avascular fibrous tissue forming a barrier between the necrotic material and underlying tissues of normal vascularity.

DISCUSSION

The finding of tubercle bacilli within living tissue cells in experimental animals or in man we believe to be pathognomonic of a low level of sensitivity. In fact, the way the tubercle bacilli seem actually to have grown within the cells of patients with a low level of sensitivity is suggestive of the "freely growing" tubercle bacilli found in the tissues of the normal guinea pig when it is first inoculated (4). In contrast to this, tubercle bacilli are never found in direct relationship with living cells in tissues from the bodies of experimental animals and humans whose level of sensitivity was high at death. This is what one would expect, for tissue culture studies show that the tubercle bacillus and its products are highly toxic to cells derived from the body of a sensitized animal (5, 6).

While tubercle bacilli may destroy sensitized cells, sensitized cells may also destroy tubercle bacilli. It has been shown that, if tubercle bacilli are injected into the peritoneal cavity of a sensitized guinea pig, 90 per cent of the microorganisms undergo lysis within an hour (7). Thus, in the highly sensitive patient, when tubercle bacilli come in contact with living cells either the cells are destroyed, or the bacilli may undergo lysis, or both of these processes may take place. This destruction of bacilli by sensitized cells probably explains the failure to find acid-fast bacilli in the lesions of our highly allergic patients, except in cavities under the special conditions described.

The avascular barrier found separating bacilli in cavities from underlying vascular tissue may be considered as preventing the growth inhibiting factors of sensitized tissue from reaching the bacilli. To this extent the bacteria are *exteriorized* from the tissues of the host and lead a "test tube" existence, incubated on the favorable medium of tissue debris containing all the elements necessary for their growth. The detachment of such material and its expectoration account

for the appearance of tubercle bacilli, often in large numbers, in the sputum of patients with a high level of sensitivity.

It was mentioned above that, in patients who have lost their sensitivity, lesions completely devoid of tubercle bacilli and lesions teeming with bacilli were often found side by side within a single histological section. Also it was stated that in such sections the bacillus-free lesions always appeared relatively old, while the lesions with numerous bacilli appeared to be recent. This difference in age of the lesions might be suggested as an adequate explanation for the difference in bacillary content. The more probable explanation becomes apparent when consideration is given to the fact that patients may lose their sensitivity during the terminal stages of the disease. The indication is clear that the older lesions were formed when the sensitivity of the patient was high enough to destroy the bacilli, while the new lesions were formed after the sensitivity had declined to a level which permitted the bacilli to flourish.

The conception of exteriorized tubercle bacilli growing within pulmonary cavities affords an additional explanation for the success of collapse therapy in pulmonary tuberculosis. As long as bacteria remain within a cavity, their products, which are destructive to sensitized tissue, can continue to produce necrosis of the outer layer of the underlying tissues. Collapse of the cavity, when it results in a reduction of the area of its wall, aids the dislodgment of necrotic material with its contained bacilli. When the bacilli with their capacity for destruction are removed from the cavity wall the tissues of repair are no longer subjected to the continuous necrosis by bacillary products and healing becomes possible.

SUMMARY

1. Tuberculous lesions in the lungs of patients who are highly sensitized at the time of death contain few or no acid-fast bacilli, except in areas of necrosis separated by an avascular barrier. On the other hand, in patients who have lost more or less completely their ability to respond to tuberculin, pulmonary lesions teeming with tubercle bacilli are found.

2. When tubercle bacilli are present in large numbers in living tissue, the level of sensitivity is low. Living tubercle bacilli and tissues of high sensitivity are incompatible.

3. The reason why the highly sensitized patient may have tubercle bacilli in his sputum is that bacilli growing on the necrotic lining of a pulmonary cavity have been *exteriorized* as far as the sensitivity factors of the body are concerned.

SUMARIO

1. Las lesiones tuberculosas de los pulmones de los enfermos que se encuentran muy sensibilizados en el momento de la muerte o no contienen bacilos ácido-resistentes o contienen muy pocos, salvo en las zonas esfaceladas separadas por una valla avascular, mientras que en aquellos que han perdido más o menos completamente su capacidad para reaccionar a la tuberculina obsérvanse lesiones pulmonares en que pululan los bacilos tuberculosos.

2. Cuando se encuentran grandes cantidades de bacilos en tejidos vivos, la sensibilidad es baja, siendo incompatibles los bacilos tuberculosos vivos y los tejidos muy susceptibles.

3. La razón por que el enfermo muy sensibilizado puede mostrar bacilos en el esputo consiste en que los que proliferan en el recubrimiento esfacelado de una caverna pulmonar han quedado *exteriorizados* en lo relativo a los factores de sensibilidad del organismo.

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DISCUSSION

Dr. William H. Oatway, Jr., Tucson, Arizona: Doctor Brosius and Doctor Woodruff are to be congratulated on presenting a very stimulating report.

There are several factors in the production of tuberculous disease which should be carefully considered. They include:

(*1*) The organism, with regard to both numbers and virulence.

(*2*) The host, with regard to both allergy and resistance. (All other factors must be equal, including portal of infection, organ involved, standards of measurement, etc.)

There is no doubt that the number and virulence (both of type and variant) of the organism can modify the course of both experimental and clinical disease. It has also been demonstrated that the relative resistance, both of species and individual, can modify the development of disease. It was formerly thought that resistance and hypersensitivity were either the same or indivisible. Now it seems certain that they can be separated, though they usually occur together.

In the present paper Doctors Brosius and Woodruff reported an inverse but regular relationship in humans between the number of bacilli in the lesions and the degree of skin sensitivity to tuberculin.

It should be possible to fit this evidence and the conclusion into the general structure of information. The authors have considered the allergy and the bacillus factors, but they have concluded that the result is due to an intolerance of the organism by tissue sensitivity.

Most of the evidence in the past has indicated that there is not a regular relationship between the type, volume or activity of human lesions and the degree of skin sensitivity. There is no connection between the degree of tuberculin sensitivity and tuberculous bronchitis, for instance: all such patients are simply tuberculin sensitive (as is any patient with a tuberculous lesion of any sort, barring those in a pregnant, moribund or exanthematous state).

There are many pieces of evidence in the literature which seem near to the present study. Tuberculins and infectious material, derived from variants of a single strain of tubercle bacillus, have been used experimentally. As a result, the number of bacilli in lesions has been found to be proportionate to the virulence of the infecting variant. The use of living or dead bacillus vaccines to prevent or reduce sensitivity, or the use of animals with failing or lost sensitivity at the time of reinfection, has given further information, both from humans and animals. The conclusions from such experiments are not regular, but there is certainly a resistance factor in the vaccinated animals which is independent of the sensitivity to tuberculin.

Using the conclusions of the present paper, desensitization or hyposensitization would be a wrong approach to treatment, with the tissues relatively anergic and supposedly unprotected; vaccination would be wise if only to have the tissues reactive.

I believe that the whole scheme of host-parasite relationship in tuberculosis is not yet evaluated. The present series of cases is worth extending so that conclusions may be drawn later and a better correlation made.

THE SIGNIFICANCE OF TUBERCLE BACILLI IN GASTRIC CONTENTS[1,2]

DAVID D. FELD[3]

The examination of gastric contents in the fasting patient for tubercle bacilli has been practiced at Muirdale Sanatorium since 1933. While it has been a routine procedure on all children since its inception, its application to adults was more gradual. By 1939 (1) this form of laboratory investigation was used extensively in adult patients to aid diagnosis, to guide therapy and to help in the evaluation of a patient before discharge. The importance of the procedure in all these phases is gradually gaining recognition, as is indicated by an increasing number of publications (2).

Examination of gastric contents for tubercle bacilli is used on all patients who deny raising sputum or whose sputum is negative. It is also used in cases where there is doubt as to the source of the sample presented. Since a single nega ive gastric aspiration is not considered conclusive, repeated aspirations are performed at various intervals. These are done on successive days, the number varying from two to six. Some patients have cultures of both sputum and gastric contents. This is particularly true of new admissions, since such a procedure expedites the diagnosis of cases with suspected active lesions.

The material used for examination consists of undiluted gastric contents aspirated from fasting patients. Only in occasional cases was it necessary to do a lavage. The stomach contents are aspirated the first thing in the morning and the material is immediately sent to the laboratory where it is prepared for culture.

Previous to 1941, culture and guinea pig inoculation were done simultaneously on all specimens. Since that time only cultures are used and guinea pig inoculation is resorted to only in special cases. Culture results are very accurate and the difference between the two procedures did not warrant continued use of the guinea pig. Culture contamination in our laboratory is down to an almost irreducible minimum and, during 1942 and 1943, out of 2,982 gastric-content cultures there were only 36 (1.2 per cent) contaminations. All specimens are cultured on three slants of Petragnani's medium, and a contamination is reported when all three tubes are involved.

The number of homogenized positive smears is small. Of 3,038 smears of concentrated gastric contents during this same period, only 147 (4.8 per cent) were found positive. This small percentage hardly makes it worth while to examine these smears, but when they are found on known cases of tuberculosis, it means that, for the time being, more aspirations are not necessary. We agree (2, 3, 4, 5) that one cannot rely on smears of concentrated specimens for

[1] From Muirdale Sanatorium, Milwaukee County Tuberculosis Sanatorium, Milwaukee, Wisconsin.

[2] Presented before the Medical Section at the 40th annual meeting of the National Tuberculosis Association, Chicago, Illinois, May 10, 1944.

[3] Santa Barbara General Hospital, Santa Barbara, California.

the detection of tubercle bacilli, and in certain diagnostic cases animal inoculations, in addition to cultures, are necessary.

The patient who has negative sputum cultures, but who has tubercle bacilli only by gastric examination, is not a so-called innocuous patient. In our survey we observed 21 such patients who on subsequent sputum examination were positive on concentrated smear or culture. Therefore, these patients can and do develop subsequent positive sputum, and they are then listed as contagious cases. A patient with a positive gastric content should be treated exactly like a patient with a positive sputum. Every effort should be made to convert his pulmonary secretions.

Before our patients are discharged it is necessary that they have negative gastric aspirations, assuming that the patient does not have adequate sputum for examination.

If examinations of the gastric contents were not done, many cases would be discharged while still active; therefore, in order for a patient to be discharged with medical advice as inactive we must have repeated negative results, or five successive negative examinations. If negative on those examinations, and if other findings warrant it, the patient is discharged with no evidence of active disease.

TABLE 1

	PATIENTS EXAMINED	TOTAL GASTRIC EXAMINATIONS	TOTAL POSITIVE ASPIRATIONS
	868	4,204	
Negative group	404 (46.4%)	1,338	
Positive group	464 (53.6%)	2,866	1,271 (44.3%)

During the past five years, 868 adults had a total of 4,204 examinations of gastric contents. Of these, 404 (46.4 per cent) had negative gastric contents; they received 1,338 examinations. The remaining 464 (53.6 per cent) cases had 2,866 examinations, of which 1,271 (44.3 per cent) were positive. (See table 1.) The number of examinations per case varied from one to 30; 28 had only one gastric aspiration—the rest had two or more. The average for the negative group was 3.3; for the positive group the average was 6.2 per case. The number of repeats depends upon the individual case, just as in sputum examinations.

Thus we have two groups of patients—those with positive and those with negative gastric contents. Each of these groups in turn is divided into three subgroups: the no-sputum group, the negative-sputum group and the positive-sputum group. (See table 2 for Positive-Gastric-Content group.)

No fine line of distinction can be drawn between these three subgroups. Occasionally patients deny raising sputum and yet the specimen they send in contains tubercle bacilli. Also there are patients who state they raise sputum, when the sample is nothing more than saliva, or secretions from a chronic nasopharyngitis so common in this locality. We also realize that, if numerous and timely sputum examinations were done, a small percentage would have been

positive that way. This is not deemed advisable, and valuable time may be lost, particularly when a simple reliable gastric aspiration can be done with culture results known in a few weeks.

Group 1—Positive gastric aspirations and no sputum: Seventy-one patients, or 15.3 per cent of the Positive-Gastric-Content group had no sputum. Of the 401 gastric aspirations, 211 (52.6 per cent) were positive. This type of patient is on the increase, and more and more of these cases are being admitted, particularly during the past four years. This is due to the Selective Service Act of October 1940, with subsequent X-ray films of all draftees, also to preëmployment X-ray examinations and the ever increasing X-ray surveys by health departments and tuberculosis organizations. Many of the cases found by these means have no evidence of clinically active tuberculosis. In some a diagnosis of active tuberculosis can be made on the basis of clinical and roentgenological findings, but in others the roentgenological findings do not settle the issue. It removes all doubt if the tubercle bacillus can be recovered, and it is more convincing to the patient if he knows the "germ" has been found and that he is not in the sanatorium just for a short period of observation but for active treatment.

TABLE 2

Positive-gastric-content group

	NUMBER AND PER CENT OF PATIENTS	NUMBER AND PER CENT OF EXAMINATIONS	NUMBER AND PER CENT OF POSITIVES
No sputum	71 (15.3%)	401 (14.0%)	211 (52.6%)
Negative sputum	111 (23.9%)	783 (27.3%)	314 (40.2%)
Positive sputum (at some time)	282 (60.8%)	1,682 (58.7%)	746 (44.3%)
Totals	464 (100.0%)	2,866 (100.0%)	1,271 (44.3%)

Group 2—Positive gastric aspirations and negative sputum: This group consists of 111 (23.9 per cent) patients who had negative sputum examinations. All sputa are cultured. They had 783 gastric examinations, of which 314 (40.2 per cent) were positive. Seventy-four (66.6 per cent) had one or more twenty-four-hour sputum cultures; 37 (33.4 per cent) had one or more forty-eight-hour sputum cultures. Of these, 20 had three consecutive forty-eight-hour cultures. On admission, 85 (76.6 per cent) were positive and 26 (23.4 per cent) were later positive after being negative on sputum culture or gastric content culture. This latter figure reveals the importance of repeating the examination. One cannot place too much reliance on one or two negative aspirations.

Group 3—Positive gastric aspirations and positive sputum: The positive-sputum group contains the largest number of patients and of gastric examinations. These cases had a positive sputum some time during the course of their treatment. Obviously some of these patients would fall into the two previously mentioned groups. That is, there were times when they turned from a positive to a negative sputum and became no-sputum cases, but they all are listed here to prevent duplication.

Of the 464 cases which had positive gastric contents, 282 (60.8 per cent) were sputum-positive some time during the course of their treatment. The total number of examinations were 1,682, and 746 (44.3 per cent) of these were positive; 86 (30.5 per cent) of these cases had a positive sputum and positive gastric content simultaneously. This occurred in 60 instances on admission and 26 times at a later date. In the 86 cases we were not certain as to the adequacy of the sputum, and therefore both sputum and gastric examinations were performed. We consider this a time-saving factor. Instead of waiting until the sputum cultures are completed and then doing gastric aspirations, the two are done at the same time. Should the sputum be negative, the aspirations will either confirm or deny.

One hundred and eighty-five (65.6 per cent) had a positive sputum from two months to eight years previous to the positive aspiration. However, excluding those few cases that were sputum-positive two, three, five and eight years previously, the average length of time was about six months.

TABLE 3

Consecutive gastric aspirations

ASPIRATIONS	PATIENTS	NUMBER OF EXAMINATIONS	POSITIVE EXAMINATIONS	PATIENTS POSITIVE ACCORDING TO NUMBER OF EXAMINATIONS	PATIENTS POSITIVE ON ONLY ONE EXAMINATION
1	62	62	292	292 (71.1%)	134
2	266	532	251	378 (92.0%)	86
3	24	72	52	395 (96.1%)	17
4	35	140	31	406 (98.8%)	11
5	24	120	16	411 (100%)	5
Total.....	411	926	642		253

158 patients were positive on more than one aspiration.

Significantly, 21 (7.5 per cent) of the 282 patients became sputum-positive after being positive at first only on gastric aspiration. This occurred on the average of about six months later. This small group of patients reveals an important fact, because, as has been previously pointed out, these cases cannot be considered as harmless, and careful observation and timely sputum examinations will find that some of these cases are sputum-positive.

The importance of consecutive gastric examinations on children has been pointed out by Poulsen and Andersen (6) but to our knowledge this has never been adequately demonstrated on adults. To do this, the initial cultures of 411 of the 464 Positive-Gastric-Content cases are recorded and no deliberate selection was made. Of the 464 cases, 53 have been eliminated because they were positive only on guinea pig or homogenized smear or both. (See table 3.)

These 411 patients had a total of 926 gastric examinations of which 642 (69.5 per cent) were positive. All of these cases were positive on one or more examinations. If one examination had been performed, only 292 (71.1 per cent) patients

would have been positive; when two examinations were done, 378 (92 per cent) patients were positive, etc., so that all the patients were positive if at least five aspirations were done. If only three examinations per patient had been done, in 16 patients (3.9 per cent) bacilli would not have been found. Of these 411 patients, 253 were positive on only one gastric examination and 158 were positive on more than one aspiration. This also reveals the importance of doing consecutive examinations; one cannot rely on one, two, or even three negative aspirations. Because of these findings we feel very confident that in those patients in whom it is impossible to determine the status of activity from a roentgenogram and in whom the sputum, if present, is negative, if five consecutive aspirations are negative on culture, most likely there is no evidence of active pulmonary tuberculosis.

The remaining 404 cases belong to the Negative-Gastric-Content group. (See table 4.)

Group 1, the negative-gastric-content and no-sputum group, and group 2, the negative-gastric-content and negative-sputum group, will be discussed together.

TABLE 4

Negative-gastric-content group

	NUMBER AND PER CENT OF CASES	NUMBER AND PER CENT OF EXAMINATIONS
1. Negative gastric contents and no sputum.....	50 (12.4%)	175 (14.4%)
2. Negative gastric contents and negative sputum.	174 (43.1%)	509 (41.9%)
3. Negative gastric contents and positive sputum...	180 (44.5%)	654 (53.7%)
Total.....	404 (100%)	1,338 (100%)

There were 224 patients who never had a positive sputum or gastric aspiration; they had a total of 684 gastric examinations. What has been said about group 1 of the Positive-Gastric-Content cases applies here. Most of these were sent in as cases of pulmonary tuberculosis for one reason or another. In a very small number of instances these patients were reported to have had a recent positive sputum on the outside, but none of these findings were confirmed by culture or guinea pig inoculation. We feel we should be able to duplicate this positive finding by the use of culture or animal inoculation, and when a series of gastric aspirations is negative as well as sputum cultures, we feel justified in recording the case as having no evidence of active tuberculosis.

Group 1 and 2 cases consist of the following: (*1*) Those with normal roentgenograms. There were 42 (18.8 per cent) such cases.

(*2*) In 114 cases, the roentgenogram revealed fibrocalcareous lesions that were considered healed, the exception being 36 cases. Nineteen of these had pleurisy with effusion. The fluid of 4 revealed tubercle bacilli on culture, and 4 were not examined. There were 17 cases that gave an X-ray appearance of activity, but this could not be confirmed by any positive aspirations or sputum. Most of these cases were discharged.

(*3*) The remaining 68 cases consist of nontuberculous pulmonary disease: bronchiectasis, 18; silicosis, 9; heart disease, 6; pulmonary carcinoma, 6; asthma, 5; pulmonary fibrosis (etiology unknown), 5; mycotic lung disease, 5; pneumonia, 4; lung abscess, 2; pulmonary infarction, 1; sarcoidosis, 2; pulmonary cystic disease, 2; pulmonary eosinophilia, 1; congenital pneumothorax, 1; benign lung tumor, 1.

Of the 224 cases, 20 (8.9 per cent) had a negative tuberculin test; 3 by Vollmer patch test, 10 by OT 1:100, 3 by PPD1 and 4 by PPD2.

One hundred and twenty-seven (73 per cent) cases had one or more twenty-four-hour sputum culture; 47 (27 per cent) had one or more forty-eight-hour sputum culture.

Group 3—Negative gastric contents and positive sputum: Of the 404 negative patients, 180 had a total of 654 gastric examinations. For the most part these examinations were done to determine the status of activity. These patients had received all types of therapy and a period was reached when they either had no sputum or were sputum-negative. Hence the gastric examinations.

The main reason that there were no positive aspirations in the group of 180 cases is because, in 157 (87.1 per cent) patients, the examinations followed by some ten months a positive sputum, and as stated many of these cases were on the road to recovery.

At the time of the negative gastric aspirations, 23 (12.8 per cent) had a positive sputum, but there were only 2.2 aspirations per patient. So it is possible to have a negative gastric content and a positive sputum. However, this does not invalidate the reliability of this procedure, and if more examinations had been done this small group would have been gastric-content-positive. There were 16 (8.9 per cent) patients who became gastric-content-negative and sputum-negative and then later became sputum-positive. This varied from two months to two years. Unstable cases of tuberculosis are likely to fluctuate like this.

In the summary of the work done by Furlong and Warren (4) at Muirdale, of 180 cases with positive gastric aspirations, the duration after the sputum had become negative was determined in 57 cases. In 90 per cent of the group, the cultures and guinea pig inoculations were negative within less than two years and averaged eleven months for the entire group. In a group of 50 patients treated by collapse, 86 per cent were negative in less than two years with an average interval of 8.5 months.

Repeated aspirations following a positive sputum have been done at an average interval of two to three months. However, in view of the above findings and continued observations, an interval of from four to six months is sufficient.

In the light of our knowledge obtained through the use of gastric aspiration we have become less dogmatic in our interpretation of inactivity according to roentgenograms, particularly those of a fibrotic nature, and, when doubt arises, gastric examination is resorted to.

In the past year and one-half it has been our policy to do five consecutive aspirations on these negative cases. If these examinations are negative by culture, the individual is considered as having no evidence of active pulmonary

tuberculosis. In the majority of these cases, particularly those of groups 1 and 2, it is wise to hold these patients for a period of observation until the cultures are completed. Of the cultures, 95.8 per cent will show growth within the first six weeks. However, the cultures are kept until eight weeks. At the end of this period, the patient is re-X-rayed and his case is reëvaluated. Most of these are discharged with no clinical evidence of active tuberculosis. In a number of instances the patient was prematurely discharged only later to be called back because of the subsequent positive culture of his gastric content.

SUMMARY AND CONCLUSIONS

In a five-year survey of 868 adult patients, a total of 4,204 gastric content examinations are recorded. Of these, 1,271 (30 per cent) specimens were positive and some of the patients had positive findings on one or more examinations.

Of the 868 cases, 404 were never positive on gastric aspiration; therefore, if only the group with positive gastric contents is considered, 464 patients had 2,866 examinations of which there were 1,271 (44.3 per cent) positive.

In all patients with the exception of the no-sputum group cultures of concentrated sputum were made.

All gastric aspirations consisted of undiluted fasting gastric contents and only occasionally was lavage necessary. The small percentage (4.8 per cent) of positive smears of concentrated gastric contents makes this method unreliable. Each specimen was cultured on three culture tubes of Petragnani's medium. Guinea pig inoculation was resorted to only in special cases. Culture results are very accurate; this is enhanced by our low contamination rate of 1.2 per cent.

The importance of consecutive examinations has been pointed out and when five are done there is little likelihood of missing positive cases; if these examinations are negative there is not much likelihood of an active lesion.

Patients who at first have only positive gastric specimens can and do develop positive sputum.

The interval of repeating these examinations need not be greater than from four to six months.

For the proper evaluation of the so-called "no-sputum" and negative-sputum cases of pulmonary tuberculosis, a series of examinations of the fasting gastric contents is necessary.

Before patients are discharged with medical advice, it is necessary that they have repeated negative gastric contents or five negative consecutive examinations.

SUMARIO Y CONCLUSIONES

En una encuesta hecha en 868 enfermos adultos se anotaron 4,204 exámenes del contenido gástrico, de los cuales 1,271 (30%) resultaron positivos mientras que algunos de los enfermos mostraron hallazgos positivos en uno o más exámenes.

De 868 casos, 404 no resultaron positivos con la aspiración gástrica, por lo cual si sólo se considera el grupo de contenido gástrico positivo, restan 464 en-

fermos en que se hicieron 2,866 exámenes, de los cuales 1,271 (44.3%) fueron positivos.

En todos los enfermos, aparte de aquellos del grupo "sin esputo," se hicieron cultivos del esputo concentrado.

Todas las aspiraciones gástricas comprendieron contenido en ayunas y sin diluir y sólo rara vez resultó necesario el lavado. Por ser tan pequeño el por ciento (4.8%) de frotes positivos del contenido gástrico concentrado peca esta técnica de poco fidedigna. Cada ejemplar fué cultivado en tres tubos del medio de Petragnani. La inoculación en el cobayo fué utilizada en casos especiales. Los resultados de los cultivos fueron muy exactos debido en particular al bajo coeficiente de contaminación: 1.2%.

Señálase la importancia de los exámenes consecutivos y cuando se ejecutan cinco hay pocas probabilidades de pasar por alto los casos positivos, mientras que si resultan negativos no hay muchas de que exista una lesión activa.

Los enfermos que al principio sólo muestran positividad en los ejemplares gástricos pueden mostrar esputo positivo, y a veces lo muestran, luego.

Los intervalos entre los exámenes no tienen que exceder de cuatro a seis meses.

Para la debida justipreciación de los casos de tuberculosis pulmonar, llamados "sin esputo" y de "esputo negativo," se necesita una serie de exámenes del contenido gástrico en ayunas.

Antes de dar de alta a los enfermos por consejo del médico, es necesario que muestren bien hallazgos gástricos negativos o cinco exámenes consecutivos negativos.

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DISCUSSION

Dr. John W. Towey, Powers, Michigan: The definition of a negative sputum represents the keystone about which is constructed our entire tuberculosis program. On it we base our classification of the disease and weigh the need for sanatorium care. It is the greatest single factor in our criteria for discharge and in our evaluation of therapy. To be effective our minimal standard must be adequate.

At the present time the American Trudeau Society and the National Tuberculosis Association are sponsoring a definition of negative sputum as follows: "A negative sputum should be called negative only when no bacilli can be found on concentration." Under this definition a patient's tuberculosis might be declared inactive by a negative smear from

a concentrate whereas the medical staff of Muirdale Sanatorium have set for themselves a standard of five consecutive gastric contents negative by culture. I think most of us will stand in awe at the immensity of their laboratory program. I admire their courage, but at the same time I feel that any controversy with it must be based on economic and technical grounds.

The excellent study presented by Doctor Feld is an attempt to evaluate the relative efficiency of collection of sputum by expectoration and by gastric aspiration. You will recall that 111 of their patients in the positive group had previous negative cultures from sputum concentrates. Excluding the examination of the gastric contents, this group could be classified as having negative sputum under our present minimal standard.

During the past two years we have been conducting a study of our negative and no-sputum cases. There were 101 patients in this group; 138 specimens of seven-day pooled sputa together with 138 specimens of gastric washings were collected from this group of patients over approximately the same time interval. Direct smears, cultures and guinea pig inoculations were made of these various specimens. The results of these examinations were as follows:

The Number of Patients and Specimens and Results of Examinations

	Totals	
	Seven-day Sputa	*Gastric*
Number of patients	101	101
Number of specimens	138	138
Average per patient	1.4	1.4
Negative by all methods	112	70
Positive slide examination	3	12
Positive by pig and/or culture	26	68
Per cent positive by pig and/or culture	19	49

CONCLUSIONS

1. Aspirated gastric contents produce more positive results than sputum concentrates.
2. Cultures of gastric aspirations correlate closely with animal inoculations.
3. Cultural methods are preferable to animal inoculations for economic and technical reasons.
4. One can be absolutely sure of the source of the specimen.
5. The fact that gastric aspirations are more productive of positive results, plus the fact that they are completely under the control of the physician should give the findings added prestige with Courts of Law and Compensating Boards.
6. It should stimulate interest in the early diagnosis of tuberculosis.
7. It solves the problem of obtaining specimens from children and patients who are not producing sputum.
8. Gastric aspiration should be a routine procedure in all cases of pleural effusion of indeterminate origin.
9. It provides a sounder procedure for recommending patients for work or rehabilitation.
10. With the present inadequacy of our minimal standard there can be no uniformity as regards the classification of tuberculosis or the evaluation of therapy.

THE DEMONSTRATION OF TUBERCLE BACILLI IN AN EMPLOYEE GROUP WITH CLINICALLY INACTIVE PULMONARY TUBERCULOSIS[1]

EDGAR M. MEDLAR[2] AND ADA CHREE REID[3]

Follow-up studies of ex-sanatoria tuberculous patients have dealt with death, relapse and ability to work and have been primarily concerned with the question of rehabilitation. The problem of tuberculous infection in man is generally recognized as extending beyond a residence in a sanatorium and beyond the surgical removal of a tuberculous lung. A recent article by Pottenger (1) has stressed the significance of laboratory tests in follow-up investigations but the incidence of the shedding of tubercle bacilli has not been established, for a routine application of culture and guinea pig inoculation was not made on smear-negative concentration of sputum and of fasting gastric contents. As those who are "clinically ill" graduate to the group of "clinically well," the "clinically silent" phase of the disease becomes increasingly important. Any study of "clinically silent" tuberculosis should include periodic roentgenograms of the chest and thorough laboratory studies of sputum and of fasting gastric contents for a period of at least five years, since in most instances a recrudescence of the disease is most likely to occur within such a period. Laboratory tests should include culture and guinea pig inoculation of all concentrates which are negative by smear. A study to determine the number of persons shedding tubercle bacilli in ex-sanatorium tuberculous employees at work was begun in 1940 and in this paper a preliminary report of the data collected to date will be presented. Since the study is still in progress no attempt will be made to deduce any clinical or epidemiological significance from the data.

Any protracted investigation which includes laboratory tests is certain to encounter difficulties. It is necessary to establish a program for serial tests which will be of considerable inconvenience to persons who are working. If sputum is raised, most individuals will coöperate to the extent of procuring a seventy-two-hour specimen when requested, but if there is no sputum, and this is the case with most ex-sanatorium patients at work, then the arrangement for the extraction of fasting gastric contents at stated intervals is somewhat of a problem. The routine of the individual is interfered with and few persons relish the procedure of a gastric lavage. However, with tact, patience, and persistence a high degree of coöperation can be obtained, provided no personal expense is involved.

The investigation centres in the Home Office of the Metropolitan Life Insurance Company, where a considerable number of ex-sanatorium patients work and where laboratory facilities are available for the aseptic collection of

[1] Presented before the Medical Section at the 40th annual meeting of the National Tuberculosis Association, Chicago, Illinois, May 10, 1944.

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fasting gastric contents. Each employee is told the purpose of the study and is assured that the results of the laboratory studies will not govern the management of his case. Further hospitalization is recommended only when serial roentgenograms or unfavorable symptoms indicate a reactivation of the disease. The employees who coöperate come to the laboratory on a prearranged date without breakfast and provision is made for a meal, without expense to them, after the gastric extraction. As far as possible, specimens have been obtained at intervals of three months. Seventy-two-hour sputum or fasting gastric samples on two consecutive days, collected in sterile containers, are sent by mail to the laboratory of the Company's Sanatorium at Mount McGregor. All specimens are concentrated and culture and guinea pig inoculations of all concentrates are made. Smears of all sputum concentrates are examined for acid-fast bacilli. If any question arises relative to a culture being one of tubercle bacilli, virulence tests are done on guinea pigs.

The data presented in this report are those collected over a three-year period from 252 persons on whom 1,381 tests were done. These persons have been grouped as follows:

I. Eighty-nine persons who had never been under medical care for the treatment of tuberculosis:

(A) Twenty-one persons in whom newly developed lesions, probably tuberculous, had been observed by roentgenograms at an annual physical examination or when examined in the Company's Medical Rest Rooms.

(B) Forty-six persons with roentgenological shadows characteristic of an old tuberculous infection when first examined and with no significant change observed in serial roentgenograms over a five-year period.

(C) Twenty-two persons who, for various reasons (contact with tuberculous cases or with manifest pulmonary lesions), had sputum examinations done to exclude the probability of tuberculosis.

II. Twenty-six patients referred to the Sanatorium as probable cases of tuberculosis and who, after thorough study, were diagnosed as nontuberculous or as having clinically inactive tuberculosis when admitted.

III. One hundred thirty-seven persons who had received treatment for clinically active pulmonary tuberculosis for a period of at least six months at the Company's Sanatorium and who were discharged to work between 1937 and 1943.

The data on group I are presented in table 1. The 21 newly discovered cases of tuberculosis were advised to have proper treatment and were not allowed to continue at work. Tubercle bacilli were demonstrated in specimens from 11 of the cases (5 by sputum, 6 by gastric). The 46 inactive tuberculous persons were all negative on one gastric examination (usually duplicate). A more thorough study of this group would probably have yielded some positive results, judging from results previously reported (2). The single positive result obtained in the

22 nontuberculous persons was from a man whose wife had pulmonary tuberculosis with a positive sputum. This man has been under observation for two years, but to date there is no roentgenological evidence of a pulmonary lesion.

The data on group II are presented in table 2 which is self-explanatory. No evidence of clinically active tuberculosis has been found in the 22 persons who have had negative tests.

The data on group III are analyzed in tables 3 to 7. All of the 137 persons had been treated for clinically active pulmonary tuberculosis. No persons with

TABLE 1

Employees with no previous Sanatorium treatment

ROENTGENOLOGICAL INTERPRETATION	NUMBER PERSONS			NUMBER TESTS		
	Total	Positive		Total	Positive	
		Number	Per cent		Number	Per cent
Total	89	12	13.5	213	27	12.7
Pulmonary tuberculosis (new cases)	21	11	52.4	98	26	26.5
Pulmonary tuberculosis* (inactive)	46	—	—	65	—	—
Nontuberculous pulmonary disease	22	1§		50	1	2.0

* All cases presented X-ray evidence of inactive pulmonary tuberculosis with no significant change for over five years.

§ Husband of an open case of pulmonary tuberculosis. No X-ray evidence of pulmonary lesion to date.

TABLE 2

Follow-up on 26 persons considered nontuberculous on discharge or clinically inactive pulmonary tuberculosis on admission

Results of tests while at work: Positive 4; negative 22 cases

SANATORIUM DIAGNOSIS OF POSITIVE CASES	COURSE SINCE DISCHARGE
1. Inactive pulmonary tuberculosis, minimal	Died—pulmonary tuberculosis
2. Abscess of lung	Died—pulmonary tuberculosis
3. Pleurisy with effusion (nontuberculous)	No clinical or X-ray evidence of tuberculosis
4. Spontaneous pneumothorax	No clinical or X-ray evidence of tuberculosis

far advanced lesions are included because the number available for study was too few to permit the gathering of sufficient data to be significant at this time. The average Sanatorium residence of the 39 minimal cases was twenty-five months and for the 46 moderately advanced was 43.5 months. At the time of discharge from the Sanatorium all but one of the 137 individuals were free from bacilli, insofar as smear examinations of concentrates of seventy-two-hour sputa were concerned. Fifteen other persons were found positive on the last culture or guinea pig inoculation prior to discharge from the Sanatorium. Of these 16 persons, 12 have had positive tests while at work.

One thousand seventy-eight tests, an average of 7.9, have been done on these persons while at work. Sixty-four of the specimens were seventy-two-hour sputa, of which 23.4 per cent were positive; and 1,014 were fasting gastric contents, of which 4.7 per cent were positive. The minimal cases had an average of 8.2 and the moderately advanced cases an average of 7.6 tests. The persons with positive tests had an average of 8.3 and those who were negative an average of 7.6.

As shown in table 3, 37.9 per cent of the cases yielded one or more positive tests. Thirty-one cases, with an average of 7 tests, had one positive; 21, with an average of 11 tests, yielded 2 or more positives. Surprisingly enough there is very little difference between the results in the minimal and moderately advanced groups. In relation to the clinical impression at the time of discharge it is to be noted that in the most favorable group, the arrested, 29 per cent of the cases were

TABLE 3

Results obtained on 137 tuberculous employees following return to work after Sanatorium treatment, by clinical status on discharge and stage of disease

STATUS ON DISCHARGE	TOTAL			MINIMAL[§]			MODERATELY ADVANCED*		
	All cases	Positive		All cases	Positive		All cases	Positive	
		Number	Per cent		Number	Per cent		Number	Per cent
Total	137	52	37.9	74	27	36.5	63	25	39.7
Arrested	69	20	29.0	42	13	30.9	27	7	25.9
Apparently arrested	12	5	41.7	4	1	25.0	8	4	50.0
Quiescent	37	18	48.6	18	6	33.3	19	12	63.2
Improved	18†	8	44.4	9	6	66.6	9	2	22.2
Unimproved	1†	1	100.0	1	1	100.0	—	—	—

§ Average Sanatorium residence—twenty-five months.

* Average Sanatorium residence—forty-three months.

† These patients continued treatment away from Sanatorium until condition became satisfactory for return to work.

positive. In the minimal group there is no correlation between clinical impression at discharge and positive tests at work above the status of "improved." There is much better correlation in the moderately advanced group down to the status of "improved." In this latter group are cases of pneumothorax who left the institution before a thorough exercise test could be given after reëxpansion of the lung, and cases of thoracoplasty who did not remain in the institution sufficiently long after thorough healing of the operative field to warrant a classification better than "improved." These patients continued their cure at home until their condition was considered satisfactory to return to work.

The data presented in table 4 show three significant facts. First, there is an appreciably higher percentage of positive cases while at work in the group that was positive at the Sanatorium than in the Sanatorium-negative group. Second, there is practically no difference in the two groups of minimal cases. Third,

a significant difference is present between the Sanatorium-positive and Sanatorium-negative moderately advanced cases.

Table 5 presents the data on the Sanatorium-negative cases in relation to the thoroughness of laboratory study. We regard a case as adequately studied if six or more cultures and guinea pig inoculations have been made on satisfactory seventy-two-hour sputum or fasting gastric specimens. The chief point of interest in these data is that adequate laboratory studies at the Sanatorium, apparently, have no correlation to the positive findings in the minimal group while at work,

TABLE 4

Results of laboratory studies on 137 tuberculous patients while at work, by stage of disease and by presence or absence of bacilli at Sanatorium

STAGE OF DISEASE	ALL CASES	POSITIVE AT SANATORIUM			NEVER POSITIVE AT SANATORIUM		
		Total	Positive at work		Total	Positive at work	
			Number	Per cent		Number	Per cent
Total	137	85	36	42.3	52	16	30.8
Minimal	74	39	15	38.4	35	12	34.3
Moderately advanced	63	46	21	45.6	17	4	23.5

TABLE 5

Results of laboratory studies while at work on cases not positive at Sanatorium, by stage of disease and by thoroughness of laboratory study at Sanatorium

STAGE OF DISEASE	ALL CASES	*ADEQUATELY STUDIED AT SANATORIUM			$NOT ADEQUATELY STUDIED AT SANATORIUM		
		Total	Positive		Total	Positive	
			Number	Per cent		Number	Per cent
Total	52	18	7	38.9	34	9	26.5
Minimal	35	14	7	50.0	21	5	23.8
Moderately advanced	17	4	—	—	13	4	30.8

* Each case had 6 or more cultures and guinea pig tests at Sanatorium.

$ Less than 6 cultures and guinea pig tests at Sanatorium.

whereas there is a correlation in the moderately advanced group. It is quite probable that adequate studies on all of the Sanatorium-negative cases would have demonstrated tubercle bacilli in several of the cases while under treatment.

Table 6 presents data relative to 34 employees who had had two or more Sanatorium residences for the treatment of tuberculosis prior to the present study. It is of considerable interest that a high percentage of the cases positive at the Sanatorium continued to be positive while at work. Of the 10 persons who were negative at the Sanatorium, 4 were adequately studied and were negative at work, while 3 of the 6 cases that were not adequately studied were positive while at work.

The data presented in table 7 are of principal interest in the relation of the demonstration of tubercle bacilli in persons at work to the type of therapy employed in the Sanatorium. The outstanding fact is the close parallelism of the minimal and moderately advanced cases which were given either conservative treatment or pneumothorax. It is to be noted that the pneumothorax group

TABLE 6

A group of 34 tuberculous employees with two or more Sanatorium residences prior to present study: comparison of results of laboratory studies at Sanatorium and at work

LABORATORY RESULTS AT SANATORIUM	STAGE OF DISEASE	LABORATORY RESULTS WHILE AT WORK		
		Total	Positive	
			Number	Per cent
Positive	Total	24	16	66.7
	Minimal	7	4	57.1
	Moderately advanced	17	12	70.6
Negative	Total	10*	3	30.0
	Minimal	5	2	40.0
	Moderately advanced	5	1	20.0

* 4 cases had six or more pigs and cultures—these were all negative at work.
6 cases had few or no pig and culture tests—three were positive at work.

TABLE 7

Results of laboratory studies while at work on 137 ex-Sanatorium patients, by stage of disease and therapeutic procedure at Sanatorium

TYPE OF THERAPY	STAGE OF DISEASE	ALL CASES	POSITIVE CASES	
			Number	Per cent
Total		137	52	37.9
Nonsurgical	Total	79	30	37.9
	Minimal	54	21	38.9
	Moderately advanced	25	9	36.0
Pneumothorax	Total	48	14	29.2
	Minimal	20	6	30.0
	Moderately advanced	28	8	28.6
Thoracoplasty	Moderately advanced	10	8	80.0

had the lowest percentage and the thoracoplasty group the highest percentage of positive cases. All but one of the thoracoplasty cases were negative by culture and pig when discharged from the Sanatorium.

COMMENT

Since this investigation has been conducted in a large city where masses of people frequently are crowded together, one might assume that the demonstra-

tion of tubercle bacilli represents an accidental finding of no significance, but careful analysis of the data does not confirm such an assumption. While only 6.8 per cent of all tests were positive, the positive results were confined to 28 per cent of the 252 persons tested. Sixty-three of the 66 persons from whom tubercle bacilli were obtained were known either (*1*) to have clinically active tuberculosis at the time or (*2*) to have had Sanatorium treatment for clinically active disease. No one would question the source of the bacilli in the "new" tuberculous cases included in the data and the most likely source in the ex-Sanatorium patients is a pathologically-active, though clinically-inactive, pulmonary lesion. This leaves only 3 cases (5 per cent) in which one might contend that the bacilli were transitory residents. Furthermore, several persons with 15 tests have been negative, whereas others with a similar number of tests have had tubercle bacilli demonstrated two or more times.

One of the surprises of the study was the similarity, insofar as demonstration of tubercle bacilli was concerned, between the minimal and moderately advanced groups. So far it appears as if the minimal cases have as difficult a time eradicating their infection as do the moderately advanced cases; but one must bear in mind that the moderately advanced cases at work represent only those in whom the disease has been brought under control. The demonstration of tubercle bacilli in ex-Sanatorium patients at work simply stresses the chronicity of the tuberculous infection regardless of the extent of the disease. From our observations it would seem logical to explain a clinical relapse of the disease in such cases on a basis of an endogenous spread from a pathologically-active, clinically-inactive focus.

The positive tests reported in this paper are to be regarded as minimal in number, since specimens were obtained for examination at infrequent intervals. A more thorough investigation would, in all probability, reveal more positive tests per person and more positive cases. Because of the many difficulties encountered, together with the added expense of such a study, it has not seemed feasible to perform as many tests as one might desire. The results obtained to date, however, are sufficient to indicate the possibilities of such a study with the inclusion of old tuberculous cases such as are presented in table 1.

The results presented in this paper would not have been obtained if culture, guinea pig inoculation, and fasting gastric contents had not been utilized. Two or more seventy-two-hour sputums were available in only 20 of the ex-Sanatorium patients, and in only 2 instances were smears of the sputum-concentrates positive for acid-fast bacilli. In most instances the number of colonies on the culture medium was less than 10, usually less than 5, which indicates that few bacilli were present. The results obtained are at variance with numerous reports in the literature that individuals rapidly "convert" their sputum after pneumothorax and after thoracoplasty. No one would question the decrease in bacillary content and amount of sputum toward infinity in most tuberculous cases after surgical intervention; but a careful and protracted study will reveal a few bacilli in "no sputum" cases more frequently than is generally thought, if the more sensitive laboratory tests are utilized. Repeated negative smears of

sputum or of gastric concentrates do not necessarily indicate that tubercle bacilli are no longer present.

The lapse of time and the volume of data gathered since this study was begun are not sufficient to warrant an evaluation of the clinical or the epidemiological implications at this time. Of the 137 ex-Sanatorium patients, only 2 have shown any increase in the extent of the disease, roentgenologically, and to date the random samples obtained in these 2 have been negative. It is hoped that this preliminary report may stimulate others to undertake similar studies. It seems logical that data of this sort may aid materially in elucidating some phases of tuberculous infection that are at present in a state of confusion, that is, exogenous reinfection, the import of a few bacilli to the individual concerned, the epidemiological significance of the "occasional positive" case, and others.

SUMMARY

This preliminary report of a study of working ex-Sanatorium tuberculous patients for the presence of tubercle bacilli is submitted with the hope that other investigators may become interested in such studies. The group is composed of minimal and moderately advanced cases. On discharge from the Sanatorium, only one case was positive on a smear of concentrated sputum and 15 others were positive by culture or guinea pig tests of concentrates of seventy-two-hour sputum or two consecutive fasting gastric contents. Twelve of these 16 persons have been positive while at work.

Forty other persons have also been positive while at work. There is practically no difference between the minimal and moderately advanced cases. Thirty-eight per cent of the nonsurgical, 29 per cent of the pneumothorax and 8 out of 10 thoracoplasty cases have been positive. The data are analyzed relative to the clinical impression on discharge, positive or negative laboratory tests while under treatment and to thoroughness of laboratory studies.

Clinical and epidemiological significance cannot be appraised at this time as the study is incomplete.

SUMARIO

Preséntase este informe preliminar de un estudio acerca de la presencia de bacilos tuberculosos en tuberculosos dados de alta del sanatorio y ya trabajando, con la esperanza de interesar a otros investigadores en estudios semejantes. El grupo comprende casos mínimos y moderadamente avanzados. Al darlos de alta el sanatorio, sólo un caso resultó positivo en un frote de esputo concentrado y otros 15 en cultivos o pruebas en el cobayo de concentrados de esputos de 72 horas, o en dos extracciones consecutivas del contenido gástrico en ayunas. Doce de los dieciséis enfermos resultaron positivos mientras trabajaban.

Otros cuarenta enfermos también resultaron positivos mientras trabajaban, sin que apenas se observara diferencia alguna entre los casos mín mos y los moderadamente avanzados. Resultaron positivos 38 por ciento de los casos no quirúrgicos, 29 por ciento de los tratados con neumotórax y ocho de 10 en que se ejecutaron toracoplastias. Analízanse los datos con respecto a la impresión

clínica al dar el alta, la positividad o negatividad de las pruebas de laboratorio mientras continuaba el tratamiento y la exactitud de los estudios de laboratorio.

No puede valorarse todavía la importancia clínica y epidemiológica de estos datos por hallarse el estudio incompleto.

All virulence tests were done by Dr. K. T. Sasano. We wish to express our appreciation of valuable technical assistance rendered by Miss Marguerite LeMoine, Miss Clara Martin, Miss Dorothy Caldwell and Mr. T. Kurko. The coöperation of the ex-Sanatorium patients was greatly increased by the tact and perseverance of Miss Mary Foley, Secretary.

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DISCUSSION

Dr. Philip H. Pierson, San Francisco, California: I am going to take as the subject of my discussion, "What are we going to do with the patients whose disease is 'clinically silent'?"

This study of Doctor Medlar's shows that many persons who have done very well clinically, at times have tubercle bacilli in their sputum. We, as clinicians, who do not have the opportunity of extensive laboratory facilities can definitely profit by the experiences of Doctor Medlar and others in showing the frequency with which this may occur.

One very probable source of this positive sputum is from tuberculous bronchiectatic pockets in the diseased area. Unless the tuberculosis has been discovered at a very early stage when complete absorption may occur, bronchial damage, plus fibrosis and resulting contraction, takes place locally, frequently leaving small or large bronchiectatic pockets and some surrounding emphysema.

Doctor Boyer, in our clinic at Stanford Medical School, carried out quite an extensive study, injecting lipiodol into the lungs of 50 or more cases of tuberculosis—all stages—and found a high incidence of bronchiectasis, frequently not associated at all with the large amounts of sputum anticipated where this condition was present in nontuberculous patients. This was true in cases of minimal tuberculosis as well as more advanced cases, and, I think, is quite often the source of sporadically positive sputum. I think people with acute respiratory infections are more subject to a positive sputum at the time of this infection than at other times, and doubtless it is due to a little local pneumonitis.

Realizing that patients may at times have a positive sputum, I think our problem is (*1*) will we isolate all cases indefinitely, or (*2*) will we educate them to live with this sequela of their disease as safely as possible for themselves and their associates? It must be the latter. We should and probably do tell them of the possibility or probability of occasionally positive days, especially if they have an acute respiratory infection. At that time they should go to bed for a short time and isolate themselves until this temporary reaction subsides. The group of elderly people who tolerate their disease very well are doubtless disseminators of tubercle bacilli during such times as these and must be watched most carefully.

It seems to me one of the most important parts in the treatment of tuberculosis is the periodic check-up of patients, including physical examination and X-ray, sputum, etc., in order that we may gauge the clinical importance of a positive sputum if it occurs, and the general progress of the patients. Often patients ask the question as to whether they will be as well as ever when they leave the sanatorium. To be honest, we must tell them all the

things they can do but warn them against a certain handicap, which, if faced cheerfully, will mean health to them and safety for others. The occasional finding of a positive sputum in a person who is clinically well must be dealt with by intensive education and guidance.

Dr. Max Pinner, New York, New York: Thorough, complete and frequently repeated bacteriological examinations, such as those reported by Doctor Feld, demonstrate tubercle bacilli in sputum or gastric contents of many patients who, by all other criteria, are clinically well and may be classified as arrested. This is not infrequently so in patients who have had what appears to be adequate collapse therapy and/or bed-rest. The clinician is, then, confronted with the question whether or not such patients require further treatment and whether or not extensive surgery, such as revision thoracoplasty, may be indicated. At the present time, no factual information is available on which such questions can be decided. It is not known whether patients fulfilling all the requirements of the classification arrested and in whom an occasional culture has been found positive have a more serious prognosis than patients in the identical clinical condition but in whom all bacteriological work has yielded negative results. In other words, nothing is known of the prognostic significance of pauci-bacillary sputum (or gastric contents). We know, of course, that patients with such findings frequently may be able to work and feel well for indefinite periods of time, as shown in the report by Doctors Medlar and Reid. We have good reasons to assume that the frequency of such findings depends more on the thoroughness of the bacteriological studies than on the quality of treatment.

During the two years from January, 1939 to December, 1940, we discharged 124 patients from Montefiore Country Sanatorium as arrested or apparently arrested. (This number includes only those in whom sufficient bacteriological work was completed during the last six months preceding their discharge.) Of this number, 68 were completely negative for at least six months before discharge. In the remaining 56 patients, an occasional positive gastric or sputum culture was obtained within the last six months before discharge.

The average observation period in both groups of patients was closely the same, namely from thirty-two to thirty-four months, that is, about two thousand patient-months for each group. During this observation period, 5, or 7 per cent, of the completely negative group experienced reactivation and 14, or 25 per cent, of the pauci-bacillary group.

The total number of patients is far too small to make the necessary subsivisions according to extent and type of lesion, treatment, sex and age. But we believe that such follow-up studies are necessary for a proper evaluation of pauci-bacillary findings in treated patients. Our studies are being continued, and it is hoped that similar observations will be reported from other institutions.

CLOSURE OF TUBERCULOUS CAVITIES[1]

JOHN LOESCH

The fact that tuberculous cavities of the lungs disappear has been known to clinicians and roentgenologists for a long time, as attested by numerous papers written on this subject. For want of anatomical proof, various theories were advanced to account for closure of the tuberculous cavities. Frequently these closed cavities were called "healed," when the majority of them were healed undoubtedly only in a clinical sense. More scarce, however, are anatomical observations and studies on the mechanism leading to their closure. The first anatomical observations were made by Laennec (1) over one hundred years ago. On careful morbid anatomical dissections and studies, he recognized that some cavities were almost completely replaced by a fibrous cicatricial tissue. Later on, only occasionally, a case was recorded—usually after spontaneous cure—more or less as a novelty. With the increased use of active therapy during the last decade, however, great interest was aroused anew on this subject. Small series were reported by Auerbach and Green (2), Pinner (3, 4), and Pagel and Simmonds (5). From a perusal of their case descriptions and illustrations, one learns that cavities heal by different mechanisms, but no opinion can be ventured as to which of these mechanisms is more frequent than the other. Pinner (6) stated therefore justly, during a discussion on this subject at the meeting of the American Association for Thoracic Surgery, held in 1941, in Toronto,—"In the present state of our knowledge, and with the extremely limited anatomical evidence available to 1941, about 33 cases including those reported here today, it is premature to venture an opinion as to the relative frequency of different mechanisms of healing. Therefore further pathological studies are urgently needed."

This report describes the detailed study of complete closure of cavities in 5 cases, with 6 cavities altogether, which were treated with pneumothorax or strict bed-rest. Four were pneumothorax cases, 3 of which had one cavity each and one 2 cavities. In the fifth case, with one cavity, the closure took place under strict bed-rest. A sixth case with one cavity, which had shrunk markedly under strict bed-rest, is included as a transitional case. All the cases were closely studied radiographically before and during treatment for various lengths of time.

METHOD OF EXAMINATION

In all cases the morphological examination was carried out after insufflation and fixation of the lungs in Kaiserling #1. A long forceps was inserted into the lumen of each stem bronchus and the latter cut in its axis between the branches of the forceps in one stroke in a coronal plane across the lobe bearing the cavity. The halves thus obtained were then cut in the same plane in slices about 1.0 cm. thick. By this technique it was possible to trace readily the course of the tributary bronchi well into the vicinity of the area containing the obliterated or re-

[1] From the Laboratory of the Homer Folks Tuberculosis Hospital, Oneonta, New York.

duced cavities. As the latter were usually halved on slicing the lobe, both portions were removed with sufficient adjacent lung parenchyma in the form of prisms, embedded in the usual manner in paraffin and cut in serial sections. Usually from 300 to 500 serial sections were made of each area containing the former cavity. This was done in order to be able to trace the bronchi continuously in their entire length toward the focus, and to obtain a clear picture of their structure and their relation to the focus proper, representing the remnant of the cavity. Serial sectioning is, in my opinion, indispensable. The examination of only a few sections is frequently inconclusive or even misleading, as in this study it was observed that bronchi which appeared to terminate near the capsule of the focus, in reality by-passed the latter or curved around it. This was revealed only in some intermediate sections on tracing them further in subsequent sections. Every third section and those between them—whenever the indication arose during histological examination—were stained with haematoxylin-eosin. Combination staining with orcein and van Gieson and Perdrau for the demonstration of reticulum fibres was used in selected sections, whenever it was thought that additional information might be gained by these methods.

CASE REPORTS

A. *Cases with Complete Cavity Closure Obtained by Pneumothorax:*

Case 1: C. B., white female, age thirty-one. The history dated back to March, 1927 with a right pleural effusion which was aspirated, and to March, 1928 with a dry pleurisy on the left. The sputum was positive for tubercle bacilli for the first time in October, 1935, but hospitalization was refused. As reëxamination showed progression of disease, the patient was admitted March 9, 1936 with bilateral tuberculosis involving the upper half of each lung, with a cavity, 4.5 x 3.5 cm., at the right apex and honeycombing in the second anterior interspace on the left side. A right therapeutic pneumothorax, started in July, 1936, was discontinued on September 21, 1936, as it did not influence the apical cavity. On film of October 23, 1936, a definite cavity, 2.0 cm. in diameter, appeared at the site of the honeycombing in the left second anterior interspace (plate I, figure 1). Pneumothorax was established resulting in reduction in size of the cavity beginning February, 1937 and finally in replacement by a dense focus on film of July 24, 1937 (plate I, figure 2). Between September 23, 1937 and November 9, 1937, three stages of thoracoplasty were performed on the right. As the sputum was not converted, and in view of the desire of the patient to have a negative sputum, a revision was done November 28, 1938. Five hours after the operation, the patient became suddenly short of breath and died four hours afterwards.

Postmortem examination, confined to the chest, revealed a thick-walled cavity in the right upper lobe with tuberculous infiltration of the adjacent parenchyma, a few discrete well walled-off tubercles and emphysema in the remaining lobes and a large haematoma in the right pleural space. The left lung was about 50 per cent collapsed by pneumothorax. On slicing this lung in different levels, a stellate scar about 1.0 cm. in diameter containing putty-like material in the centre was found in the midportion of the upper lobe (plate I, figure 3). This was easily identified as being the relic of the former cavity on comparison with the X-ray films.

Microscopically this focus was composed of granular debris in the centre, staining faintly bluish with haematoxylin-eosin. In various areas, collections of fine calcium granules

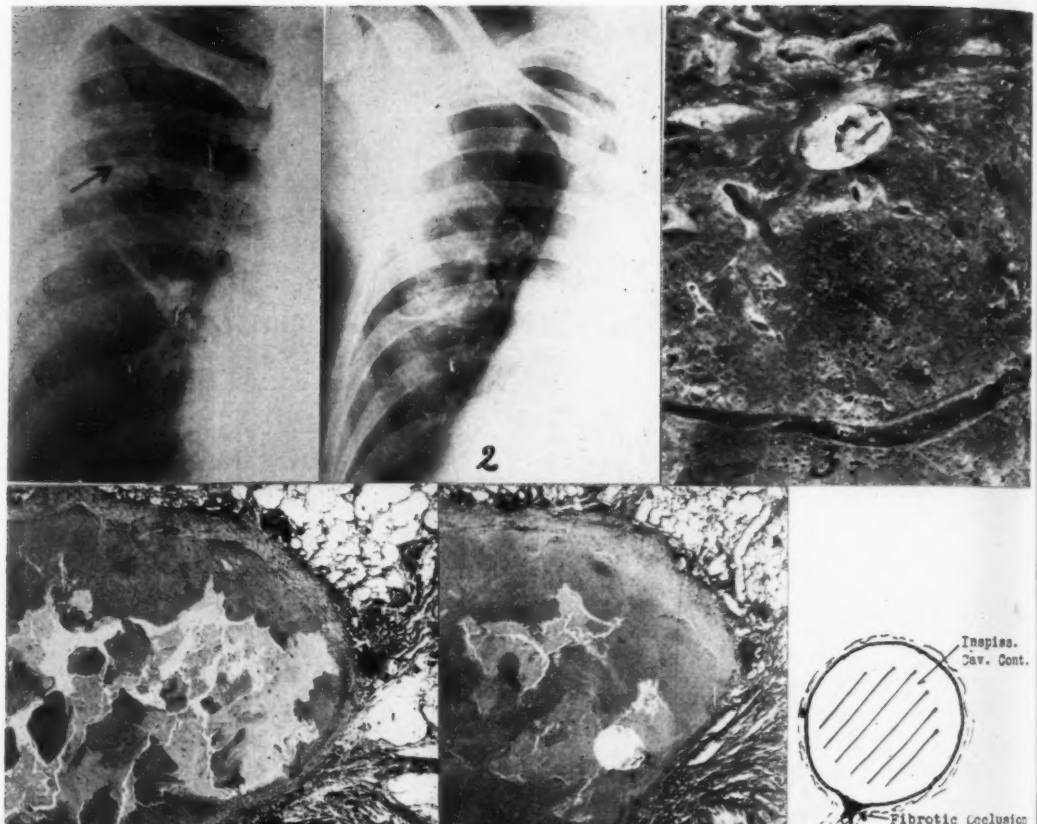

PLATE I

Case 1: C. B. Roentgenograms demonstrate the left upper lobe cavity on film of October 23, 1936 (FIG. 1) before the institution of therapeutic pneumothorax and its replacement by a dense focus on film of July 24, 1937 (FIG. 2).

FIG. 3. Section of the left upper lobe through the dense focus, representing the former cavity, on film of July 24, 1937.

FIGS. 4 & 5. (Magnification 7×). Photomicrographs of the dense focus with the tributary bronchus in different levels. Figure 4 illustrates the dilated patent bronchus. In figure 5 the latter is markedly reduced. The latter picture was taken from a section close to the blind end of the bronchus.

FIG. 6. Schematic drawing of the closed cavity, the fibrotic occlusion of cavitary outlet and the blind end of the tributary bronchus.

were discernible. This central core was surrounded by a corrugated caseous layer more solidly arranged towards the periphery and staining bright red with eosin. On staining with orcein a few single elastic fibres and thrombosed vessels were demonstrable in this zone. This in turn was well walled-off by a layer of hyalinized connective tissue densely arranged in the medial portions and more loosely in the periphery from which connective tissue strands radiated out towards the intact lung parenchyma. On silver impregnation, a densely felted network of reticulum fibres was demonstrated permeating the inner adjacent caseous zone. They stained dark brown and were much thicker at the periphery. In both capsular layers was seen an occasional giant-cell and in the outer one, that is, the loosely arranged one, a caseous but fibrosing tubercle, thus representing a phase of healing. Examination of serial sections showed a dilated bronchus (plate I, figure 4) which was normal in all sections but terminated blindly and cone-shaped, close to the connective tissue capsule. The mucous membrane was everywhere demonstrable but showed several pouches at the blind end. As no other bronchi around this focus were seen, this was unquestionably the bronchus that drained the former cavity.

Summary: The mechanism of closure of this cavity was about as follows Due to relaxation of the parenchyma, by pneumothorax, the cavity contracted gradually in a concentric manner, resulting simultaneously in concentric narrowing and approximation of the outlet, within the wall of the cavity, and finally closure by connective tissue. In the course of closure, the wall of the cavity was gradually replaced by a fibrotic tissue, walling off the granular debris and caseous tissue centrally located. The tubercle outside the fibrotic capsule was either present before the latter developed and was not included in the walling off process or some bacilli might have passed through the capsule by way of lymph spaces or lymph vessels producing a tuberculous lesion, which, too, finally regressed under pneumothorax treatment.

Case 2: G. D. K., white female, age thirty-five, was admitted June 11, 1936 with bilateral disease diminishing in the lower third on both sides with a cavity measuring 4.5 x 4.5 cm. in the lower part of the right upper third (plate II, figure 1). Pneumothorax was induced on July 6, 1936, on the right, followed by a pneumonolysis on August 12, 1936. In January, 1937, when the collapse was about 80 per cent, the cavity (plate II, figure 3) could no longer be seen, but rarefaction suggestive of cavity and several honeycombed areas above the first interspace on the left made their appearance. During 1937 there were no great changes. In the first ten months of 1938 she had several "colds," an especially severe one in October. As an X-ray examination revealed increase of disease in the upper half of the left lung with a moderate-sized cavity, an attempt to reëxpand the right lung was started, with fluid appearing in the pleural space. The last refill was given November 5, 1939. By April, 1941, the right lung was nearly completely reëxpanded to the periphery. An increased density remained which was interpreted as pleural thickening (plate II, figure 4). The cavity on the left had increased in size measuring 8.0 x 11.0 cm. During the following months the patient became more and more cachectic and expired October 6, 1941.

Postmortem examination revealed chronic pulmonary tuberculosis, with a huge cavity in the left upper lobe; hyperplastic tuberculous bronchitis of the left upper lobe bronchus; tuberculous bronchopneumonia, left lower lobe; chronic fibrous pleurisy, left; parenchymatous degeneration of heart, liver and kidneys; oedema of the lower extremities; acute dilatation of the right heart.

Right Lung: This was emphysematous in all lobes. The fissures between the lobes were obliterated by thin adhesions. On dissection of the lobes, the right upper contained in its middle third, somewhat beneath the lateral visceral pleura and closely above the obliterated fissure between upper and middle lobe, an oval shaped whitish caseous area, 1.2 cm. broad and 2.0 cm. long extending towards the hilum (plate II, figure 5). It was well demarcated by a fibrotic capsule that was paper thin in the upper half with several angular processes radiating into adjacent parenchyma, however, about 2.0 mm. thick and grayish, in the lower one. Three bronchi were traced to close proximity of the old cavity, which had changed into a large compact focus.

On microscopical examination of the serial sections, the focus was caseous throughout containing calcium granules in numerous areas, especially in the periphery. It was enveloped by a thin fibrotic capsule which extended as a fibrotic cord from the lateral pole towards the thickened fibrotic visceral pleura. The thickening at the lower end, which appeared grayish on macroscopical examination, was due to pigmented atelectatic parenchyma situated between the capsule and visceral pleura of the fissure. On tracing the above mentioned three bronchi individually in serial sections, it was found that their lumina were dilated in their entire course up to close proximity of the cavity wall. One terminated blindly in mushroom shape, as the result of weakening of the wall due to former tuberculous involvement at the portion close to the cavity wall (plate II, figure 6). Its floor was partially lined by epithelial cells. On one end it showed caseation, which extended as a fine streak through the entire thickness of the cavity wall, but was permeated by fibroblasts from both sides of the bordering capsular tissue. The other bronchus gave off rectangularly a smaller branch, which became gradually obliterated. Its lumen, however, was everywhere epithelialized and from its floor extended a triangular fibrotic band to the cavity wall, thus indicating the former outlet. The third bronchus showed in its main course the same characteristics as the former two; but it gave off also in its peripheral portion a secondary branch (plate II, figure 7). This coursed for some distance along and was pressed against the cavity wall. Its lumen was slit-like and filled with debris and polymorphonuclear cells and terminated finally at the outer capsule layer. Its walls showed diffuse caseous bronchitis (plate II, figure 8). Medially to the main focus, small foci were seen, discrete or confluent, but well walled-off and almost completely calcified. Several typical epithelioid cell tubercles with caseation in the centre were noticed in the emphysematous parenchyma above the main focus.

PLATE II

Case 2: G. K. Roentgenograms demonstrate the right upper lobe cavity on film of May 20, 1936 (FIG. 1) before institution of pneumothorax and its reduction and disappearance on films of November 27, 1936 (FIG. 2) and of January 29, 1937 (FIG. 3), respectively, during pneumothorax.

FIG. 4. This demonstrates the partially reëxpanded lung with a dense focus representing the former cavity.

FIG. 5. Section of the right upper and middle lobes through the dense focus. The fissure between the lobes is obliterated. The visceral pleura is thickened and slightly indented opposite the focus.

FIG. 6. Microscopical section through the longitudinal axis of a bronchus terminating blindly in a mushroom shape at the outer layer of the capsule of the focus.

FIG. 7. Microscopical section of a dilated bronchus (a) and a small bronchus (b) at the point of branching off from the former. The small bronchus shows diffuse caseous bronchitis, terminates blindly at the outer layer of the capsule of the focus and is pressed in its entire length against the latter (FIG. 8).

FIG. 9. Schematic drawing of the closed cavity and the three patterns of closure.

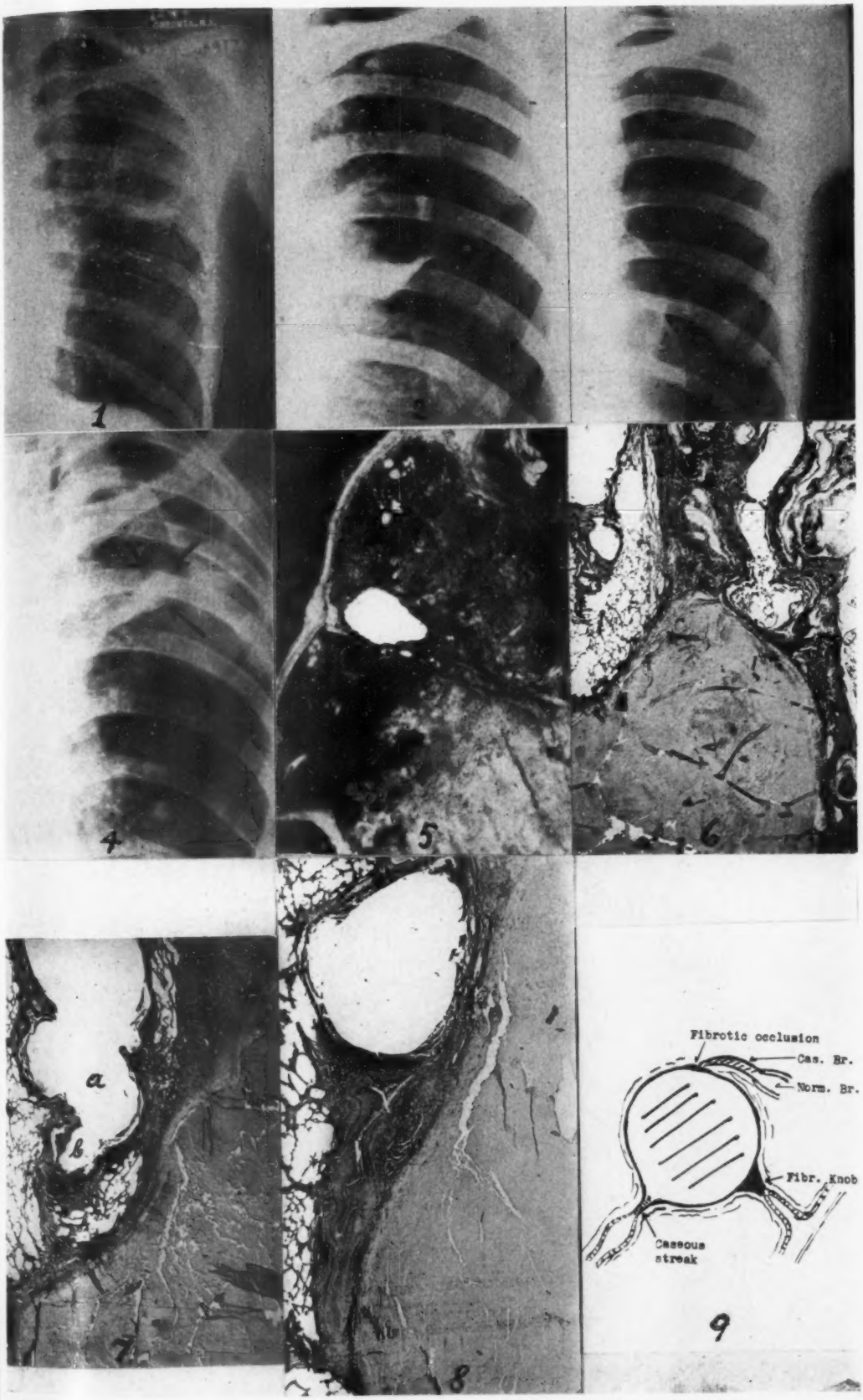
1
2
3
4
5
6
a
b
7
8
Fibrotic occlusion
Cas. Br.
Norm. Br.
Fibr. Knob
Caseous streak
9

PLATE II

Summary: This cavity, situated at the periphery of the parenchyma of the upper lobe was drained by three bronchi. Under pneumothorax a marked relaxation of the lung took place resulting in gradual shrinkage of the cavity, with simultaneous approximation of the inner surfaces of each of the three outlets within the cavity wall, terminating finally in the closure of the lumina. Then, partial epithelization took place at the blind end in one bronchus, and complete one in the other, but somewhat away from the outer boundary of the cavity wall, as the obliterating fibrosis of cavitary outlet extended into the adjacent bronchial portion. That such was the course of events is borne out by the fact that the third bronchus was patent in this segment. As soon as closure of all three outlets had occurred, the caseous material retained in the cavity became inspissated. The foci medially to the main focus were unquestionably of the same age as the former cavity. However, those in the emphysematous tissue above the main focus appeared recent and were in all probability of bronchogenic origin, developing during reëxpansion.

Case 3: S. G., iron moulder, age forty-eight. His illness dated back to the summer of 1935. As in December, 1935 a roentgenogram (plate III, figure 1) revealed a cavity 7.0 x 5.0 cm. in the right upper lobe, pneumothorax was induced. In the spring of 1937, a pneumonolysis was done in two stages, complicated by an effusion which was present ever since. He was discharged December 1, 1938, with a negative sputum. As it reverted in March, 1939, he was readmitted with 50 per cent collapse of the right lung complicated by tuberculous empyema and a small cavity in the left apex. A pneumothorax induced for the latter lesion failed because of broad surface adhesions. As the tuberculous empyema became secondarily infected by streptococci and needle tract abscesses began to appear, tube drainage was instituted November 22, 1941. His course was progressively downhill and he died January 11, 1942.

Postmortem examination revealed a huge cavity in the left upper lobe and a tuberculous pneumonia with beginning cavity formation in the left lower lobe; pleural effusion on the left; empyema of the right pleural cavity, drained; amyloidosis of the liver, spleen and kidneys.

Right Lung: This was about the size of two fists. Both fissures were obliterated. The upper and middle lobes were markedly shrunken, resting in a cap-like manner on the apex of the lower lobe. They felt firm on palpation and were diffusely black pigmented. The upper lobe was about half the size of the middle one. Closely beneath the cartilage-like thickened pleura, about 1.5 cm. below the summit of the upper lobe, there was a grayish, well walled-off kidney-shaped area measuring 2.0 cm. across and 1.0 cm. in vertical diameter (plate III, figure 4). In addition, there were a few millet-seed-sized lesions of the same type scattered in the lateral portion above the fissure. The middle lobe contained also a few small foci. Its main bronchus and large order branches in the peripheral third were completely filled by inspissated caseous material. The lower lobe was negative except for an area of numerous coalescent pea-sized nodules of putty-like material in the mediastinal phrenic angle. On tracing the course of the upper lobe bronchus and its branches by cutting the lobe in four different levels, the apical branches revealed in many points marked narrowing of the lumen, alternating with saccular dilatations and terminated in a drumstick-like manner in the atelectatic apex. The antero-lateral branch readily identified because of its wide lumen, became almost obliterated in close proximity to the anterior

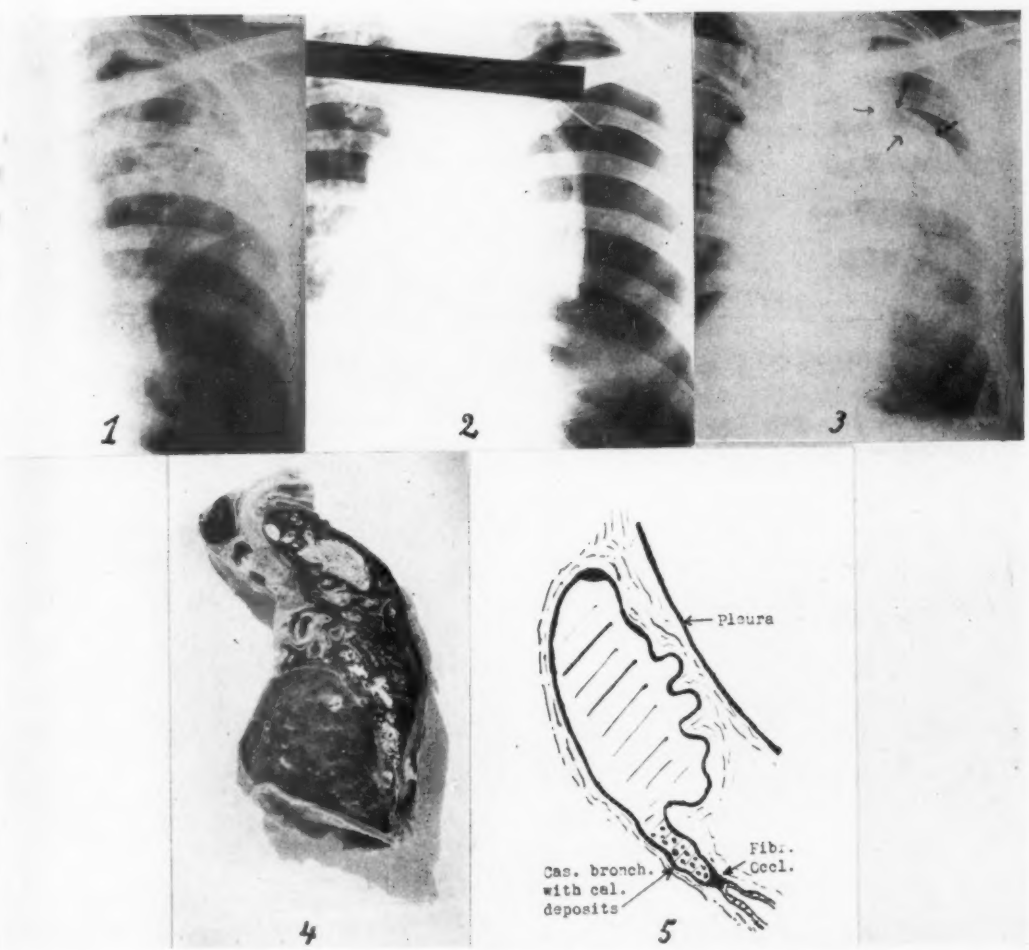

PLATE III

Case 3: S. G. Roentgenograms demonstrate the right upper lobe cavity on film of December 17, 1935 (FIG. 1) before the institution of pneumothorax and its reduction on film of August 26, 1936 (FIG. 2).

FIG. 3. This demonstrates the partially reëxpanded lung with a radiolucent area underneath the visceral pleura at the apex on film of August 28, 1940.

FIG. 4. Coronal section of the right lung with caseous focus in the right upper lobe corresponding to the radiolucent area in figure 3. The lobes are interadherent. Caseous foci are present in the pigmented shrunken upper and middle lobes.

FIG. 5. Schematic drawing of the closed cavity, the tributary caseous bronchus with calcium deposits and the fibrotic occlusion at the transition of the occluded bronchus into its normal portion.

half of the inspissated focus. As it was assumed to have been the draining bronchus of the former cavity it was used as a landmark in the examination of the serial sections. The postero-lateral branch was also traced close to the focus.

On microscopical examination, the focus was about the same as those in the previous cases. Its capsule, however, was folded, showing convex bulges alternating with concave pouches. The antero-lateral bronchus, which was thought on macroscopical examination to have drained the former cavity, became dilated beyond the point of almost complete obliteration close to the capsule and terminated beneath the pleura. The marked narrowing seen in several points was produced by folding of the mucous membrane or by the cartilaginous plates which, covered intimately by the epithelial lining, projected with one end in a knuckle-like manner into the lumen. The bronchial cartilage frequently showed beginning or almost complete ossification with bone marrow formation. In the submucosa there were, in many areas, tubercles seen in the state of regression.

In sections from the posterior half of the focus the former outlet of the previous cavity was readily identified (plate III, figure 5). It was about 2.0 mm. thick and 8.0 mm. long, bordered above and below by a layer of connective tissue, the space between which was filled with caseous calcarious material. At the beginning it was markedly narrowed due to contraction of the surrounding cavity wall. Then it became somewhat widened and tapered off finally in the most peripheral portion, consisting of a streak of scar tissue only, opposite which the postero-lateral branch terminated blindly with many small pouches. These were caused by concentric, stellate ridges of scar tissue which finally became epithelialized. The architecture of the patent portion of this bronchus is about the same as the antero-lateral one. A few small bronchi, apparently branches of the large one that once drained the cavity, were also filled with caseous material but nowhere were connections with the main focus demonstrated. Laterally and below the latter, there were numerous, small, well encapsulated foci with varying degree of calcification which were undoubtedly remnants of tuberculous infiltrations in the parenchyma.

Summary: Under pneumothorax a gradual contraction of the cavity accompanied by folding of the cavity wall, occurred. As the extensive caseation in the inner layers of the cavity extended into the draining bronchus with a large lumen, the latter became obliterated by contracting scar tissue at the point of transition of the caseous tuberculous bronchial wall into the normal mucous membrane, before the caseous material distally to it was expelled. It is also possible that during progressing shrinkage of the cavity some of its caseous content was squeezed into the lumen of the bronchus already involved by caseous bronchitis and there became calcified. The regressing tubercles in the submucosa of the bronchi were undoubtedly relics of the former tuberculous bronchitis.

Case 4: L. S., white female, thirty years old. Illness began insidiously after the birth of a child in May, 1935. On April 15, 1936, she was admitted to this hospital with a large cavity in the apex of the left lower lobe and infiltration and beginning cavity formation in the middle third of the right lung. Pneumothorax was induced on May 15, 1936, on the left, but was abandoned as ineffective because of broad adhesions. On May 5, 1937, the cavity on the right measured 1.5 x 2.0 cm. (plate IV A, figure 1). In addition, there was an area of infiltration somewhat laterally and below and a radiolucent area about 1.5 cm. in diameter at the anterior end of the fourth rib. A successful pneumothorax was induced on this side on May 10, 1937. The cavities were not demonstrable by X-ray for the first time on February 21, 1938 (plate IV A, figure 2) and thereafter. After

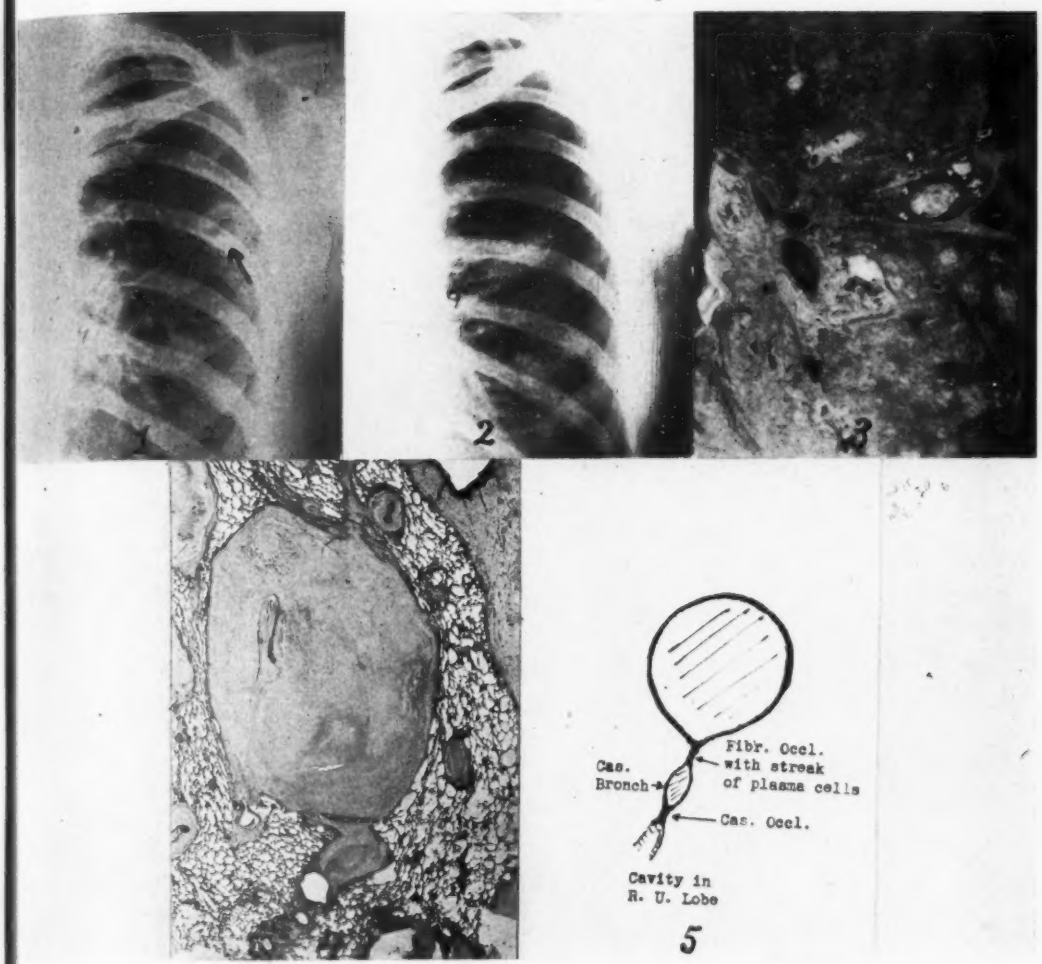

PLATE IV A

Case 4: L. S. Roentgenograms demonstrate a cavity in the right upper lobe, an area of infiltration somewhat laterally and below, and a radiolucent area in the right middle lobe on film of May 5, 1937 (FIG. 1) before introduction of pneumothorax and their disappearance on the film of February 21, 1938 (FIG. 2) during pneumothorax. The cavity in the right upper lobe is replaced by a ground-glass appearing shadow and the radiolucent area in the middle lobe by a dense focus.

FIG. 3. Coronal section showing the caseous focus representing the former cavity (figure 1) in the right upper lobe. A few calcified foci are present in the adjacent tissue. Note the indented, thickened, visceral pleura.

FIG. 4. Microscopical section through the caseous focus (figure 3) representing the former cavity in the right upper lobe and the tributary bronchus.

FIG. 5. Schematic drawing of the closed cavity and the two fibrotic occlusions of the tributary bronchus, one at the site of the former cavitary outlet and adjacent bronchial segment and the other at the transition of the caseous bronchus into the normal portion, with caseous material between the two occlusions.

pneumothorax had been reëstablished on the left on October 6, 1936 because of haemoptyses, fluid appeared which remained positive for tubercle bacilli until July, 1938. A mixed empyema and a bronchopleural fistula made their appearance in the same month. This was treated with a rib resection on August 3, 1938. Fluid appeared on the right side in October, 1938. The lesion progressed steadily on the left. The patient died suddenly December 27, 1938.

Postmortem examination revealed extensive tuberculosis with cavity formation, bronchopleural fistula and empyema on the left; amyloidosis of liver and spleen; acute dilation of the heart.

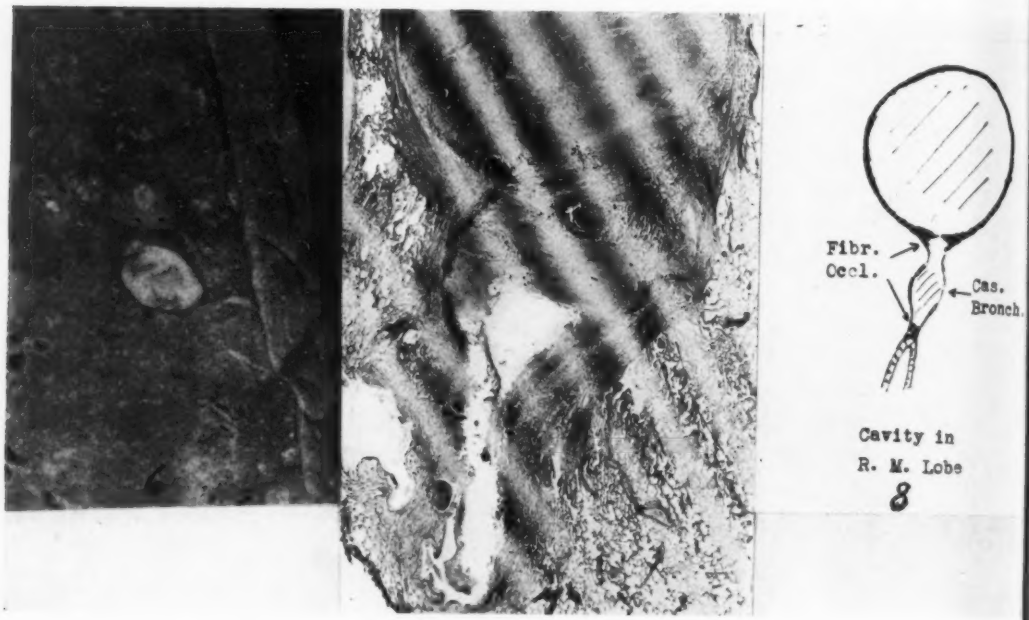

PLATE IV B

FIG. 6. Section of the caseous focus representing the dense focus, (plate IV A, figure 2) in the middle lobe. Its capsule is sharply delineated and pigmented.

FIG. 7. Microscopical section of the caseous focus (figure 6). Note the convergence of the capsule fibres towards the centre of the cavitary outlet and the occlusion of its lumen by them. A cartilage is clearly seen in the bronchial wall.

FIG. 8. Schematic drawing of caseous focus and the fibrotic occlusions at the cavitary outlet and at the bronchus proper.

Right Lung: This was partly collapsed; its pleura fibrotic and thickened. The fissures were obliterated. On slicing the lung in 1.0 cm. thick layers in a vertical-caudal direction, three oval shaped areas, each well demarcated, were found. One, measuring 1.0 cm. x 0.75 cm., was situated in the lateral portion of the middle third of the shrunken middle lobe (plate IV B, figure 6). It had a gray and caseous appearance. Another one, 1.5 x 1.0 cm., well walled-off by a pigmented capsule and corresponding to the cavity seen in the roentgenogram, was found in the upper lobe closely above the lateral end of the fissure (plate IV A, figure 3). On palpation its consistency was firmer than that of the former, being rubber-like. In addition, there were a few tiny discrete foci scattered in the

adjacent parenchyma. A third large focus, above which the pleura was indented, was found anteriorly to the latter. From its lateral pole extended a fibrotic strip towards the pleura and merged at its peripheral end with the pleura. In the first two foci the tributary bronchi were readily traced to their vicinity. In the third, that is, in the most anterior one, none was found. The lower lobe showed numerous areas of bronchopneumonia with beginning cavity formation.

Focus in the middle lobe: On microscopical examination, this (plate IV B, figure 7) was composed of caseous material containing fine calcium granules in the centre and coarser ones in the periphery. The caseous material was enveloped for the most part by a cellular or collagenous connective tissue capsule. In some points the latter was very thin and the parenchyma adjacent to it was atelectatic or infiltrated by tuberculous granulation tissue. At the medial pole the capsule merged directly with the bronchus. The capsular outlet, however, was occluded by wedge-shaped fibrous tissue formation projecting from either side and fusing in the centre. The surface of this obliteration, bordering the bronchial lumen, was covered by caseous tissue. The adjacent bronchial portion was almost completely replaced by tuberculous granulation tissue. However, remnants of cartilaginous plates were still demonstrable. Its outline was somewhat globular but became narrower as soon as the normal portion of the bronchus appeared. On staining with orcein, elastic fibres of lung tissue and the outline of vessels were clearly demonstrable at the periphery of the caseous focus but none in the centre.

Summary: This caseous focus with beginning cavity formation became walled-off by a connective tissue capsule under pneumothorax. Under simultaneous contraction the capsular outlet obliterated and the lumen of the tributary bronchus distended in globular shape due to retention of caseous material and weakening of the wall by the tuberculous process, but narrowed at the point of the transition of the segment with caseous bronchitis into the normal bronchial tube.

Focus in the upper lobe (plate IV A, figure 4): This, in contrast to the one just described, was enveloped by a thick fibrotic hyalinized capsule from which a felted network of reticulum fibres radiated into the central area of caseation. The lung parenchyma adjacent to the outer layer was moderately infiltrated by lymphocytes. Also, an occasional giant cell was seen but no epithelioid cell tubercles. As, at the medial pole, the cells and fibres of the capsule changed their course from a circular to a perpendicular one, a structure was produced resembling that of a bottleneck. They were densely crowded and infiltrated in the most central portion by plasma cells arranged in a longitudinal line parallel to the long axis of the bronchus. Proximal to this point the bronchus in which the mucosa was completely destroyed, but in which remnants of bronchial cartilage were still demonstrable, was filled with caseous material for a short distance and then obliterated by scar tissue. This in turn was lined with cuboidal cells which gradually merged with the ciliated cells of the patent normal bronchus. Above the main focus there were several small oval-shaped ones which were also well walled-off by a fibrotic capsule but were calcified in the centre.

Summary: Under pneumothorax the cavity and its capsular outlet contracted concentrically and the latter became obliterated after approximation of its inner surface. As this course of events occurred before all the caseous material in the cavity was expelled, the retained material filled the cavity lumen completely after further shrinkage of the cavity wall. The same mechanism took place in

the bronchial outlet and later the outer surface of the obliterated portion became epithelialized.

B. *One Case of Complete Cavity Closure Developed on Bed-rest:*

Case 5: G. B., a thirty year old housewife, had spasms of cough accompanied by wheezing and retraction of the mediastinum to the right dating back to 1938. In addition, she had repeated attacks of laryngitis with aphonia in 1941, followed by fatigability and weight loss. After an haemoptysis of 6 ounces in November, 1942, she entered her local county sanatorium. A roentgenogram of November 12, 1942, revealed a mixed exudate and productive infiltration above the second anterior rib with a cavity 3.0 x 3.0 cm. on the right, shift of the trachea and mediastinum to the right and contraction of the lower lobe. The left lung was normal. Sputum was positive on smear for tubercle bacilli. She was put on strict bed-rest. By May 5, 1943, the cavity was still demonstrable, but was markedly reduced in size (plate V, figure 1).

She was transferred to this hospital in August, 1943. Bronchoscopy revealed almost complete occlusion of the right main bronchus below the orifice of the right upper lobe bronchus with pus exuding from a tiny bronchial opening. A roentgenogram showed contraction of the right lower lobe and emphysema of the right upper lobe, shift of the trachea and mediastinum to the right, scattered infiltrations throughout the right upper lobe with a well demarcated ring shadow (plate V, figure 2) measuring 1.0 x 1.5 cm. in the first anterior interspace. In the sputum four bacilli were found on concentration.

On August 24, 1943, a right pneumonectomy (Dr. J. Maxwell Chamberlain) was done followed by thoracoplasty in October, 1943. Convalescence was uneventful; sputum was converted.

On gross examination of the lung, the upper lobe merged directly with the middle one as only a small fissure was demonstrable laterally. The lobes were very emphysematous. The lower lobe was cone-shaped due to shrinkage.

On slicing the upper lobe at different levels, a few circumscribed tubercles were seen, scattered over the apex, most pronounced in the summit. In about its middle third, 3.0 cm. from the summit and about 0.5 cm. from the surface of the lateral visceral pleura which was indented at this point, there was a circumscribed elongated caseous focus (plate V, figure 3) about 0.5 x 1.5 cm. in diameter, well demarcated by a fibrotic pigmented capsule. This was undoubtedly a cavity remnant, as on stereoscopic examination its location corresponded to that of the cavity present in November, 1942. Two small patent bronchi were traced to its immediate vicinity.

On microscopical examination, the focus was composed of a caseous core enveloped by a capsule, the inner layer of which consisted of typical tuberculous granulation tissue with giant cells. Its outer layer, however, was fibrotic though diffusely infiltrated by lymphocytes. On tracing the above-mentioned bronchi in serial sections, the one leading towards the posterior half of the focus showed tuberculous bronchitis with tubercles in the submucosa and an intact stratified squamous epithelial lining with the lumen patent. After gradual conical narrowing and final complete obliteration, the most peripheral portion extended as a homogeneous fibrotic tortuous string, in which occasionally a remnant of a cartilaginous plate was discernible, towards the focus terminating finally in its capsule. The other bronchus, leading to the anterior half, showed first an intact bronchial wall and a patent lumen, but then the latter became abruptly occluded by scar tissue (plate V, figure 4) beyond which the lumen was completely filled by a string of epithelioid cells (plate V, figure 5), thus indicating the previous course of the former. Close to the capsule

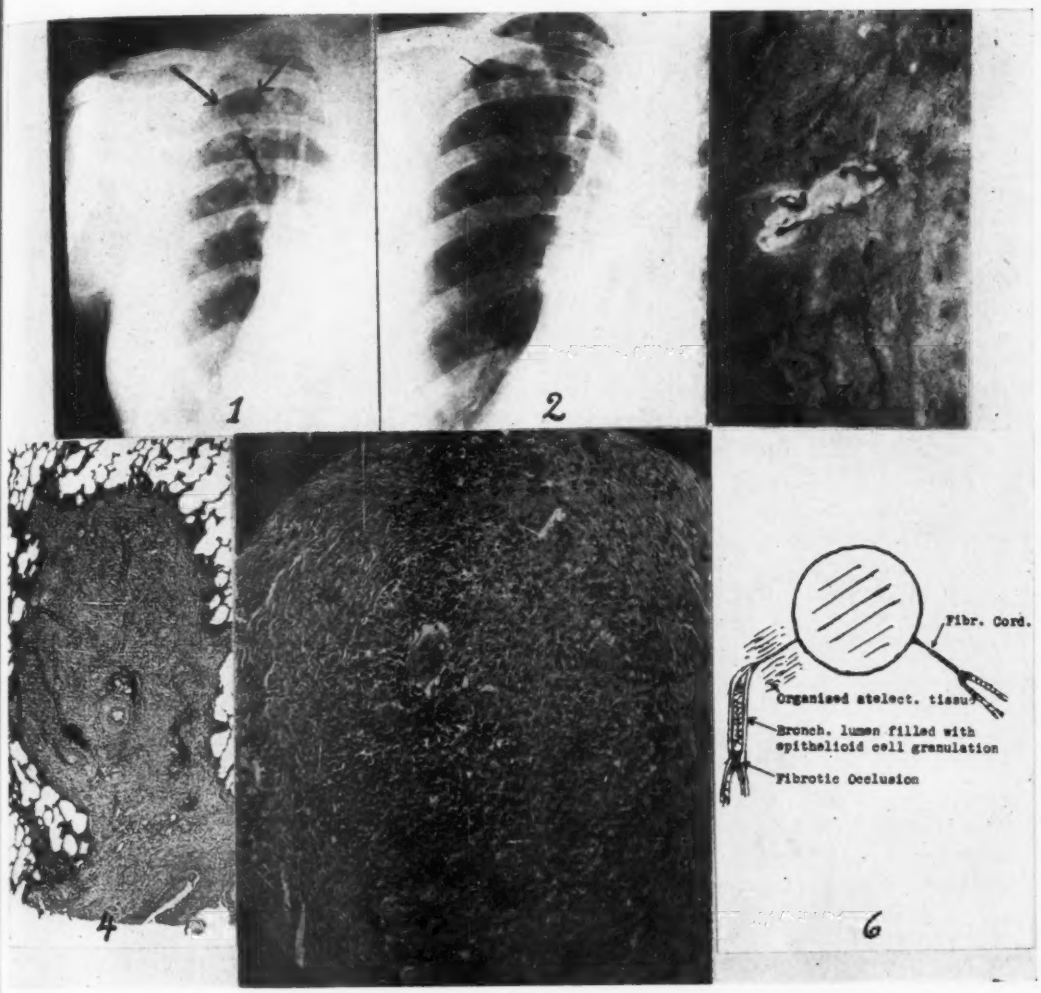

PLATE V

Case 5: G. B. Roentgenograms demonstrate the cavity in the right upper lobe on film of May 5, 1943 (FIG. 1), and a ring shadow on film of August 2, 1943 (FIG. 2).

FIG. 3. Section through the caseous focus of the upper lobe corresponding to the cavity in figure 1.

FIG. 4. Microscopical section of the proximal segment of the tributary bronchus. Its entire lumen is obliterated by fibrotic tissue.

FIG. 5. Microscopical section of a segment of the same bronchus distal to that shown in figure 4. The lumen is completely filled by epithelioid cell granulation tissue. At the left a portion of the bronchial wall can be seen.

FIG. 6. Schematic drawing of the inspissated caseous focus and of the lesions forming the occlusions of the two bronchi that formerly drained the cavity.

the occluded bronchus turned almost rectangularly towards the focus and this portion was then enveloped by a thick mantle of organized atelectatic lung parenchyma.

Examination of the lower lobe confirmed, in general, the findings obtained by clinical, bronchoscopic and radiographic examination.

Case 6: W. W., a thirty-seven year old mechanic, suffering from diabetes, moderately severe for the last seven years, was admitted on May 30, 1940, with a productive cough and loss of weight since March, 1940. The sputum was positive for tubercle bacilli. A roentgenogram showed a homogeneous cloudiness of the right upper lobe and a patch of infiltration approximately 3.0 x 2.0 cm. in the midportion of the left upper lobe. Therapeutic pneumothorax was induced on the right but was abandoned on the first of October, because of severe attacks of fever. Four bronchoscopies performed during the last five months of pneumothorax were inconclusive. As a biopsy taken during the fifth bronchoscopy on November 13, 1940 showed anaplastic carcinoma, a one-stage pneumonectomy (Dr. J. Maxwell Chamberlain) was done Nobember 25, 1940. The postoperative course was uneventful. Roentgenogram taken February 10, 1941 showed a slight increase of the pulmonary tuberculosis on the left. Feeling that this was due to retraction of the left lung into the right hemithorax, a thoracoplasty was done April 4, 1941 on the right, to counteract this overexpansion of the left lung. In December, 1941 symptoms of obstruction from metastases in the lymph nodes around the trachea and oesophagus made their appearance. The patient succumbed to this carcinoma on December 12, 1942.

Left Lung: On a coronal section in the axis of the stem bronchus, a cavity was halved, somewhat anterior to the entrance of the tributary bronchus (plate VI, figure 1). This cavity was situated in the middle third of the upper lobe about 1.0 cm. beneath the lateral portion of the visceral pleura. The latter was thickened and showed a deep indentation. From the deepest point, a thickened strip of fibrotic tissue extended toward the cavity wall. The cavity, measuring 1.0 cm. in diameter, was almost completely filled with a grayish-red debris. The bronchial branch leading to this cavity was embedded in a thick envelope of connective tissue. Apparently the cavity had markedly shrunken as judged from the appearance and deep indentation of the pleura. Below the cavity the parenchyma was atelectatic. In the lingula and medial to the cavity there were several small caseous tuberculous foci. The apical portion of this lobe, and the entire lower lobe were normal.

On histological examination of serial cross sections of the bronchus (plate VI, figure 2) draining the cavity, its lumen was somewhat narrowed at the point of branching off from the upper lobe bronchus. The submucosa was infiltrated with plasma cells and lymphocytes and contained epithelioid cell tubercles, but with the mucosal epithelial lining above them intact. A short distance distally the bronchus formed a saccular dilation from the medial end of which a rather large bronchus (plate VI, figure 3d) branched off supplying the lung parenchyma medially to and below the cavity, and from the lateral end a smaller one (plate VI, figure 3c) coursing in a straight line to the cavity. It was at its entire length about 1.0 mm. in diameter increasing gradually in close proximity to the cavity wall and measuring about 2.0 mm. within the latter. The mucosa and submucosa were almost completely replaced by a vascular tuberculous granulation tissue that had eroded and destroyed even the cartilaginous plates. This bronchus was enveloped in its entire length by a thick mantle of collagenous connective tissue. The cavity itself revealed a well developed capsule at the lower half from which stellate scars radiated into the adjacent emphysematous lung parenchyma. They extended usually along vessels and exhibited in the centre typical tuberculous granulation tissue. The upper half of the cavity was bordered by a layer of loose connective tissue that was diffusely infiltrated by lymphocytes and polymorphonuclear cells. Opposite the point of the pleural indentation it was

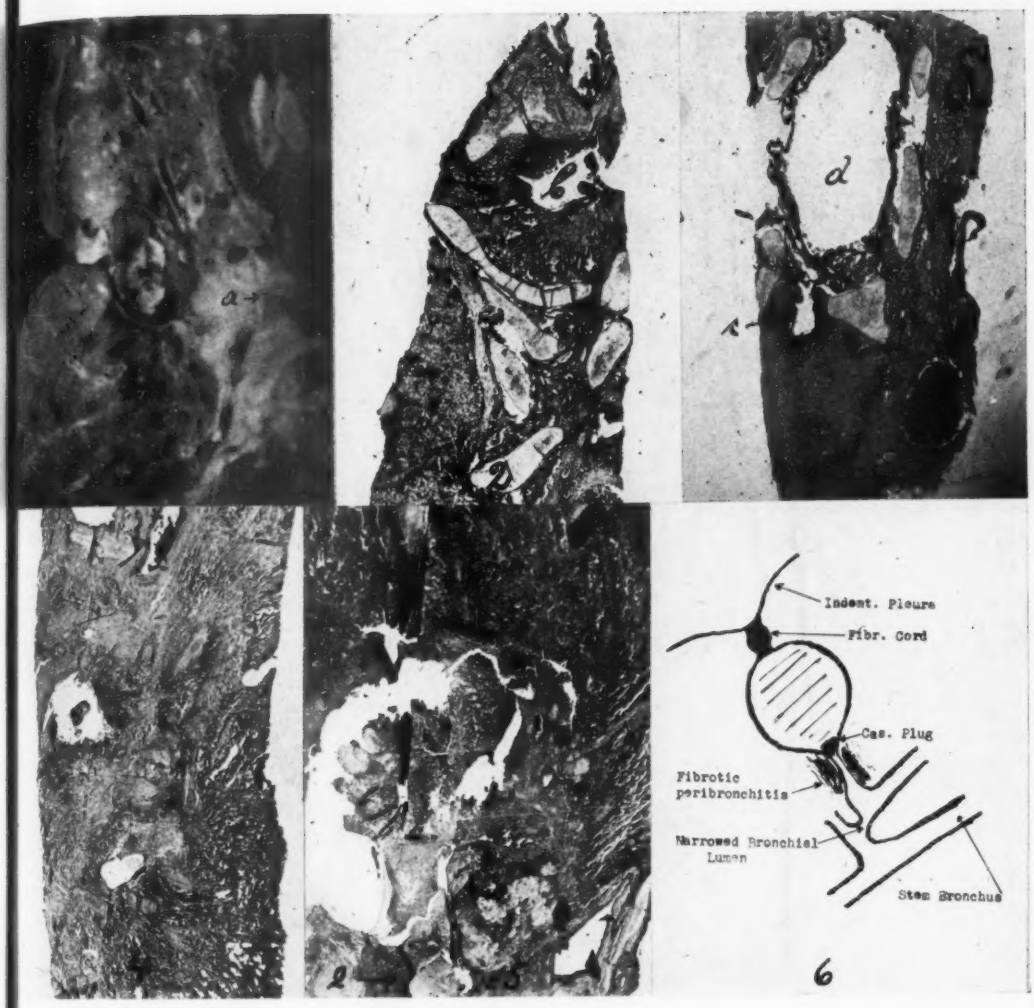

PLATE VI

Case 6: W. W. FIG. 1. Section through the markedly shrunken cavity containing caseous material in the lumen. At "a" there is the branching off point of the first order bronchus of the upper lobe bronchus, one branch of which constitutes the bronchus tributary to the cavity. The latter bronchus is embedded in a thick mantle of fibrotic tissue. Note the deep indentation of the visceral pleura and the fibrotic cord extending from the former to the cavity.

FIG. 2 to FIG. 5. Magnification 5×. Photomicrographs of three cross sections, designated as "b", "c" and "d" of the bronchi indirectly or directly tributary to the cavity.

FIG. 2. Cross section of the first order bronchus "b" of the upper lobe bronchus, somewhat distally to the branching off point "a" in figure 1, corresponding to the area marked "Narrowed bronchial lumen" in the schematic drawing.

FIG. 3. Cross section of the two branches of the former (figure 2) a short distance beyond its bifurcation. The letter "c" represents the most proximal segment of the tributary bronchus and "d" the lumen of the other branch which is dilated due to bronchiectasis. Note the reduction in the diameter of the lumen and the destruction of the mucosa by the tuberculous process in "c".

FIG. 4. Cross section of the distal portion of the tributary bronchus corresponding to the tip of the caseous plug "e" in figure 5 that projects from the cavity content into the bronchial lumen. A small portion of the caseous plug is seen in the centre of the bronchial lumen. The diameter of the bronchial lumen is larger at this point than at the point of branching off.

FIG. 5. Photomicrograph of the cavity filled with caseous material which projects as a plug "e" into and filling the bronchial lumen completely. In the left half of the cavity lumen some caseous material is missing as it came off from the slide during staining.

FIG. 6. Schematic drawing of the shrunken cavity and the relationship of its tributary bronchus to the bronchus of the first order and the upper lobe bronchus.

bordered by a cord of hyalinized connective tissue that extended from the lateral pole to the indented pleura. There were large blood vessels subpleurally and black pigment in the remaining peripheral portions. The cavity itself was lined by a pyogenic layer composed of polymorphonuclear cells and debris with the exception of the area around the outlet where it was lined by a thick layer of stratified squamous epithelium. The cavity lumen was almost completely filled with caseous material, serum, black pigment and polymorphonuclear cells (plate VI, figure 5).

This material also extended into the cavity outlet occluding the latter completely in a cork-like manner (plate VI, figure 5e). Above the cavity there was a broad zone of atelectatic parenchyma with tuberculous bronchitis of the smaller bronchi.

Summary: The mechanism at work that resulted in shrinkage of the cavity as evidenced by the diminution in its size, the stellate scars radiating from the cavity wall and the deep indentation of the pleura opposite the cavity, was about as follows: The lumen of the first order bronchus was narrowed at the point of branching off from the upper lobe bronchus. Thus, the air entering through it during inspiration and passing into the saccular dilatation was more readily transmitted into the bronchus and its branches supplying the parenchyma medially and above the cavity than into the narrowed branch leading to the cavity, which branched off almost at a right angle and was held in a rigid position by an enveloping connective tissue mantle. Indeed, very little if any air entered the cavity itself as it was almost completely filled with necrotic tissue and leucocytes that blocked in a stopper-like manner the cone-shaped outlet. Thus the retracting forces around the cavity were greater than the expanding ones and diminution in the size of the cavity resulted.

That the cavity was of long standing is evidenced by the fact that the cavity was lined around the outlet by stratified squamous epithelium and a broad cord of connective tissue extended from the lateral pole of the cavity towards the pleura with which it fused.

DISCUSSION

During respiration the lungs are passively kept in an expanded position by the pull of the chest. This is brought about by the movements of the ribs, sternum and diaphragm. The extent of the expansion is greater during inspiration than during expiration. The bronchi, due to their intimate association with the lungs, are subjected more or less to the same changes. They become elongated and dilated during inspiration, shortened and narrowed during expiration. They serve not only as the pathways for the air, but also for the secretions and infected material and perform the very important function of removing the latter by ciliary and peristaltic movements from the diseased lungs. Because of this intimate contact they become, especially when they are bronchi tributary to draining cavities, almost always afflicted by the same disease to a various degree and extent.

When the lungs are freed of this pull, as in therapeutic pneumothorax, they retract and finally collapse due to their elasticity, including in this process existing cavities. About the same mechanism, differing only in degree, is at work when a

patient is on strict bed-rest, provided that only uncomplicated cavities are present to which no obstruction exists in the tributary airways, in contradistinction to tension cavities.

In general, factors which influence the closure of cavities are: location, duration, thickness of the cavity wall, size, calibre and number of draining bronchi and possibly also the allergic state of the cavity tissue. The mechanism at work, resulting in the closure of cavities in the cases presented, is for the most part one of shrinkage of the cavity with simultaneous contraction, approximation and final obliteration (*1*) of the cavity outlet or (*2*) of the tuberculous bronchus at the point of transition into the normal portion by fibrotic tissue, or (*3*) at both these points when caseous material is retained in the diseased bronchial portion between them. The first mode is clearly presented in case 1. The cavity was of short duration and the draining bronchus was not involved by tuberculosis. It was also found in each cavitary outlet leading to the bronchi 3 and 2, in case 2. In outlet 2, its occlusion extended beyond the focus in the form of a triangular knob towards the intact bronchus. In outlet 3, the tributary bronchus showed diffused caseous involvement. Outlet 1 and the adjacent bronchial portion were markedly contracted, containing still a caseous streak in its lumen.

The second type of closure was seen in case 3 in which the inspissated, caseous material, which was partially calcified, extended for some distance into the lumen of a large caseous bronchus filling it out completely. The same mechanism prevailed also in case 5. In this case, however, one bronchial lumen was in its entire length, distal to the fibrotic occlusion, filled by epithelioid cell granulation tissue; the other by a fibrotic cord, representing the healed phase of lesion seen in one.

The third type of closure was found in the two cavities of case 4.

The occlusion at the aforementioned points (*1*), (*2*) or (*3*) took place before closure of the cavities was completed. This is borne out by the fact that the foci contained varying amounts of inspissated caseous material, depending in general on the size of the cavity. This caseous content became partially calcified in cases 1 to 4.

In case 6 the outlet of the shrunken cavity was occluded by a plug of cellular debris contiguous to the content of the cavity. The development and preservation of this condition was favored by the tuberculous endobronchitis, absence of bronchial peristalsis, narrowing of the lumen of the tributary bronchus and conversion of the latter into a rigid tube by fibrotic peribronchitis. In addition, air entering during inspiration through the narrowed mouth of the first order bronchus apparently passed readily on into the wide, straight-upwards-coursing branches and probably not at all into the bronchus draining the cavity, as this branched off almost at a right angle. This I consider a contributory factor of pathological-physiological importance.

In none of the inspissated foci in cases 1 to 4 were tubercle bacilli found either by the Ziehl-Neelsen or by the fluorescent method. Whether or not the culture method would have yielded a negative result can, of course, not be stated as the lungs were fixed before they were dissected. As oxygen and moisture, essential

for the growth of tubercle bacilli, were markedly diminished or almost absent, it is probable that the tubercle bacilli died off under these conditions after a certain length of time.

Radiolucent, ring-shaped shadows found in the roentgenogram, in the presence of a sputum strongly positive for tubercle bacilli are, as a rule, read unequivocally as cavities. Great difficulty may, however, be encountered when an irregularly outlined radiolucent area persists in the course of the closure of a cavity. If this is interpreted as a residual cavity, as it actually happens in the majority of such cases, an unindicated form of therapy might be decided upon. The former interpretation was given in cases 3 and 5 of our series. A thoracoplasty was planned in case 5 after removal of the lower lobe. In both cases this area proved to be an inspissated cavity on examination of the lung specimen.

SUMMARY

1. A detailed study of complete closure of 6 cavities from 5 cases and a marked shrinkage of one cavity in a sixth case, added as a transitional one, is reported.

2. Of these 6 cavities, 5, seen in 4 cases, became closed during treatment with pneumothorax and one on strict bed-rest only. The latter treatment resulted in shrinkage of the cavity also in the transitional case.

3. The mechanism at work leading to closure of the cavities and the diversified final patterns of the pathology in the individual cases after accomplished closure are presented. They were for the most part one of shrinkage of the cavity with simultaneous contraction, approximation and final obliteration (*1*) of the cavitary outlet, or (*2*) of the tributary tuberculous bronchus at the point of transition into the normal portion by scar tissue, or (*3*) at both these points with caseous material retained in the tuberculous portion between them. After closure at these three points, the cavities shrank further and the content retained in them became inspissated and finally partially calcified.

4. Shrinkage of the transitional case occurred by a plug, occluding the outlet of the cavity, favored by the endobronchitis, absence of peristalsis, fibrotic peribronchitis and the rectangular position of the diseased bronchus, largely preventing passage of air from the main bronchus.

SUMARIO

1. Preséntase un estudio pormenorizado del cierre absoluto de 6 cavernas en 5 casos y la marcada contracción de una caverna en un séptimo caso agregado por representar la fase de transición.

2. De esas 6 cavernas, 5 correspondientes a 4 casos se cerraron mientras recibían tratamiento con neumotórax, y una exclusivamente con el descanso en cama. El último tratamiento también obtuvo la contracción de la caverna del caso de transición.

3. Preséntase el mecanismo que condujo al cierre de las cavernas y las diversas formas definitivas que tomó la patología en cada caso, después de obtenerse el cierre, consistiendo principalmente en reducción de la caverna con contracción

simultánea, aproximación y obliteración definitiva: (*1*) del conducto de la caverna, o (*2*) del bronquio tuberculoso tributario en el punto de transición a la porción normal por tejido cicatricial, o (*3*) en ambos puntos con substancia caseosa detenida en la porción tuberculosa entre ambos. Después de cerrarse en esos tres puntos las cavernas se contrajeron todavía más y el contenido retenido en ellas se espesó y por fin calcificó parcialmente.

4. La contracción del caso de transición se debió a una obstrucción que obturó la salida de la caverna, favorecida por la endobronquitis, ausencia de peristaltismo, peribronquitis fibrósa y la posición rectangular del bronquio afectado, lo que impidió en gran parte el pase de aire del bronquio principal.

The writer wishes to express his appreciation to Dr. Kornel Terplan for perusal of the manuscript and to Mrs. Beatrice Geary for typing it.

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BOVINE TUBERCULOSIS IN THE UNITED STATES[1]

Its Conquest and Its Effect on Public Health

H. R. SMITH[2]

I was glad to accept the invitation to appear on this program because I feel sure that you, as members of the medical profession, will be interested in the story of how the cattle of the United States became infected with tuberculosis, how it has now been almost completely eliminated, increasing the production of meat and dairy foods, and how this has helped to reduce materially the incidence of the disease in man.

Cattle brought from Spain to America shortly after its discovery by Columbus were inferior in type, but were later improved by the introduction of breeding stock from England, Scotland, the Channel Islands and the Netherlands. While these importations were largely responsible for the early improvement of our cattle, some of them were infected with tuberculosis unbeknown to the purchasers, for this was long before Koch isolated the germ and prepared tuberculin supposedly as a cure but now used as a detector of the disease.

These early importations gave the disease to our native cattle through the medium of water-tanks and feed-bunks until many became infected, particularly in the northern half of the United States. It was much less prevalent in southern cattle because, until within the last forty years, Texas fever was very prevalent in the south and many of the relatively few imported cattle sent there died from this cause. Now that Texas fever has been eliminated, except in a very few quarantined counties in Texas and Florida, it is safe to move cattle north and south for either breeding or feeding purposes.

The distribution of improved seed stock, while it has given us a good quality of cattle in nearly all parts of the country, spread tuberculosis among feeding as well as breeding cattle, though to a less extent in the western range territory than on farms where cattle are in closer contact.

FEDERAL MEAT INSPECTION

It was not until 1906, when our present system of Federal meat inspection was established by act of Congress, that we had any comprehensive and accurate means of determining the increase in the incidence of the disease. As in man, it cannot be detected from outward appearance except in very advanced stages. We have seen many cattle in excellent flesh that reacted to the tuberculin test and on autopsy showed diseased lymph nodes. I well remember as a student at Michigan State in 1895, in the early days of the tuberculin test, when the college herd was tested, much to our surprise a number of fine-looking cattle reacted and showed lesions when slaughtered. Later, while in charge of the

[1] Presented at a meeting of the Michigan Trudeau Society, Grand Rapids, Michigan, May 25, 1944.

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livestock work at the Universities of Nebraska and Minnesota, we had the same experience, as also in our own purebred herd in Hillsdale County, Michigan.

Federal meat inspection, because of its thoroughness, is not only a safeguard to meat consumers, but the carefully tabulated records indicate increases and decreases in the number and percentage condemned for various diseases. Of the total number of cattle slaughtered each year under Federal inspection in the United States, the percentage retained for tuberculosis increased from 0.9 per cent in 1908 to 2.35 per cent in 1916. Because of its slow progress, there are many cattle infected that have not yet reached the stage where the lesions are visible, and the incidence of the disease was much higher than is indicated by the percentage retained—those that show visible lesions on postmortem examination.

LIVESTOCK INDUSTRY IMPERILLED

As the percentage retained increased more than two and one-half times in those nine years, there was good reason to be concerned. The peak loss was in 1917 when 40,746 cattle and 76,807 hogs, infected by the milk and droppings of cattle, were condemned for tuberculosis under Federal inspection in the United States—a waste of 35,000,000 lbs. of meat that year, of which half was at Chicago. In addition, many parts of carcasses were condemned as inedible. It was the consistent increase in losses that threatened the future of the industry and caused the Chicago livestock market interests to form a committee in 1916 and to subscribe a fund to engage the writer to conduct an educational campaign informing producers and legislative bodies of this threat in the hope that something could be done to relieve the situation. The original committee consisted of E. C. Brown, President of the Chicago Live Stock Exchange; A. G. Leonard, President, Union Stock Yards & Transit Company, Chicago; Thomas E. Wilson, President Wilson & Company; G. F. Swift, Vice-President Swift & Company; Edward Morris, President Morris & Company; and E. R. Gentry, Armour & Company. The western railroads also aided in this project.

While the large number of cattle and hogs condemned for tuberculosis was directly a packers' loss, it was indirectly a loss to producers because buyers, knowing in advance that a certain percentage would be condemned, bid a little less to allow for this anticipated loss.

This disease in cattle and hogs had become so prevalent that many thought its eradication quite impossible. Numerous individual breeding herds had been tuberculin-tested and the reactors slaughtered, but the losses at market centres continued to increase. I recall distinctly that in 1917, in a conference with the late Henry Wallace, editor of Wallace's Farmer, father of Vice President Wallace, in order to secure coöperation in publicity, he made this remark: "Smith, don't you think it is an impossible undertaking?" That was the attitude of many.

In 1916 and 1917 numerous shipments of infected cattle were traced back to the farms from which they came and the owners notified. The breeding cattle on these farms could not be tuberculin tested for lack of Federal and state funds, but it did create concern. The only solution seemed to be a concerted move

by the United States Department of Agriculture and the various states to be provided with adequate funds to test systematically all breeding cattle, in order to remove eventually the cause in fattening cattle and hogs.

LEGISLATION

On March 4, 1917, the Congress appropriated $75,000 for tuberculosis eradication, but no provision was made for indemnity on reacting cattle slaughtered.

In 1917 we supplied information to Congressman C. H. Sloan of Nebraska, author of a bill providing an appropriation of $1,000,000 for tuberculosis eradication.

At the first hearing before the House Agricultural Committee January 14, 1918, the writer stated that progress could not be made without partial reimbursement on reacting cattle slaughtered. So large a number of cattle were then infected, many breeders would otherwise be put out of business. It was pointed out that this was also a public health measure and every tax payer should be willing to help. A clause was inserted to provide that the Federal Government would pay one-third of the loss to a limit of $25.00 on grades and $50.00 on purebreds, provided the state or county would pay at least an equal amount. Soon after, numerous state legislative hearings were held and appropriations made to meet the conditions of the Federal law.

The House of Representatives voted $250,000, the amount recommended by the U. S. Department of Agriculture. Resolutions adopted by a large number of livestock organizations, urging a larger appropriation, were sent in and the Senate increased this to $500,000 for indemnity and operating expense which, after a public hearing attended by livestock men from the various states, was later approved by the House.

ANNUAL HEARINGS

Each year thereafter hearings were held in Washington attended by representatives of producer organizations, market groups, state departments of agriculture and medical associations. Charts were prepared to show the progress in cattle testing under the able direction of the U. S. Bureau of Animal Industry and the state departments with the resultant decrease in losses. These annual hearings were continued until 1928 when Congress appropriated $6,000,000. By 1932 this was increased to $6,505,800. The state and county appropriations totaled that year approximately $13,000,000. By 1935 the Federal, state and county appropriations totaled $26,792,179, the maximum amount for any year with substantial decreases since, according to needs, until now a relatively small sum is required.

SIXTY-DAY RETEST

The State Live Stock Sanitary Boards of Minnesota, North Dakota and Montana passed a sixty-day retest regulation effective May 1, 1917, which was followed by other states. While a member of the Minnesota Board previous to 1917, I found in some instances that purebred cattle shipped in from other

states came with the required health certificate, but reacted a few weeks later. They had obviously been inoculated with tuberculin privately to nullify the official test a few days later. A number of cattle breeders were then unsympathetic to the test. The retest, requiring another official test sixty days after reaching destination, unless the cattle originated from a tuberculosis-free accredited herd, not only stopped the "plugging" of the test, but encouraged breeders to clean up to facilitate sales and interstate movement.

TUBERCULOSIS-FREE ACCREDITED HERDS ESTABLISHED IN ALL STATES

It seemed most important to apply the tuberculin test to the purebreds herds first.

Upon the invitation of the Chicago Live Stock Exchange, a conference was held at the Saddle & Sirloin Club, Chicago, December 3, 1917; it was attended by the Chief, Dr. John R. Mohler, and other representatives of the Bureau of Animal Industry, 35 state veterinarians, 3 directors chosen by each of the cattle registry associations, agricultural editors and the members of the Sanitary Committee of the Chicago Live Stock Exchange. It was called for the purpose of starting a nation-wide movement for the establishment of tuberculosis-free accredited herds. At this conference the writer, as Chairman, was instructed to appoint a committee of 5 breeders, 2 representing the beef interests, 2 the dairy interests and one the range interests, to meet with a committee of 5 Bureau officials and state veterinarians for the purpose of drafting regulations for accrediting herds. These regulations were later approved by the U. S. Live Stock Sanitary Association, the U. S. Bureau of Animal Industry and the various states. A herd was officially accredited when less than 0.5 per cent reacted on the last complete test.

INTRACUTANEOUS TEST

On March 1, 1920, the U. S. Bureau of Animal Industry officially recognized the intracutaneous test for the first inspection in accredited herd testing. This made it possible to test at least three times as many cattle with the same force of men as were previously required for the subcutaneous, or temperature, test. Soon after this, the intracutaneous method was approved for all tests.

On February 1, 1921, there were approximately 50,000 herds of cattle under Federal and state supervison and 28,108 herds of breeding and dairy cattle had passed one successful test. A total of 5,502 herds were fully accredited.

The testing of individual herds under the accredited-herd plan in widely scattered communities throughout the United States was also helpful in creating better public sentiment in those communities, and many owners of grade herds who became familiar with the work requested the test.

COUNTY AREA TESTING

The first draft of the regulations for county area testing was prepared by Dr. J. A. Kiernan, Chief in charge of Tuberculosis Eradication work for the U. S. Department of Agriculture, and the writer during the spring of 1921.

These were patterned after the regulations previously adopted for accrediting individual herds. The plan was later slightly modified by the U. S. Live Stock Sanitary Association and adopted by the U. S. Department of Agriculture.

During the month of November, 1921, federal veterinarians in charge of tuberculosis eradication in the north-central and eastern states assembled at Hillsdale, Michigan, where each took part in the testing of all cattle in Hillsdale County, which was completed in a period of two weeks. This was for the purpose of standardizing the technique in the application of the tuberculin test and to demonstrate the possibilities of a concerted effort to test all of the cattle in a county during a short period of time. The Hillsdale Board of Supervisors had appropriated $3,000 for area testing, the first County Board to make such an appropriation.

One veterinarian with a car and driver was assigned to each half township. Evening sessions were held where the men had an opportunity to give observations. The experience gained by this demonstration, which was in charge of Doctor Kiernan, Doctor Wight, assistant chief, and Dr. T. S. Rich, Lansing, Michigan, proved valuable to the men in the various states from which they came.

The rules adopted for accrediting counties prescribed that all breeding and dairy cattle must be tuberculin tested. Feeding cattle in separate yards, having no contact whatever with the breeding herd, were not required to be tested. If the owner permitted feeding cattle to mingle with the breeding cattle, or to drink from the same water-tank, it was necessary to have them tuberculin tested. No indemnity was paid on steers or grade bulls.

Provision was made for placing under quarantine all herds in which reactors were found, and these infected herds were retested at intervals until no more reactors were disclosed. If more than one per cent of all the cattle tested in any county reacted, it was necessary, under the rules and regulations, to apply the test again on all cattle in the county one year later. When it was found on succeeding tests that less than 0.5 per cent of all the cattle in the county reacted, such a county was eligible to be designated as a modified accredited area.

PREMIUM ON HOGS FROM ACCREDITED COUNTIES

When plans were first formulated for the testing of all cattle under the county area plan, a large number of packing companies consented to the offer of a premium of 10 cents per hundred above market price on hogs produced in accredited counties. At that time the average loss on the entire slaughter of hogs in the United States caused by tuberculosis was approximately 10 cents per hundred and prices were depressed to that extent at all markets where tuberculosis in hogs was prevalent. The premium was offered as a recognition of the increased value of hogs practically free from tuberculosis and for the further purpose of encouraging counties to undertake this method of eradicating tuberculosis. Many of these companies voluntarily continued the plan for a period of four years after the termination of the three-year trial period. A total of approximately $3,000,000 was paid to the producers in premiums on hogs from accredited counties during that time.

This premium helped materially in arousing public sentiment to the need of eliminating tuberculosis from livestock. The offer was based on the assumption that if the cattle in a county are free from tuberculosis, the cause of tuberculosis in hogs will be removed. As found later, this proved to be true as to condemnations in hog carcasses, but to a less extent in localized lesions, largely the result of infection with the avian type through the common practice of permitting poultry to mingle with hogs. No doubt this premium was an important reason why county area testing progressed so rapidly in the cornbelt states where hog raising is an important industry. During the period of years in which the premium was paid, the average loss on the entire slaughter of hogs caused by tuberculosis was reduced from approximately 10 cents to 3 cents per hundred live weight.

THE EMPLOYMENT OF LIVESTOCK COMMISSIONERS AT OTHER MARKETS

During the years 1920 and 1921, meetings were held at several other important markets for the purpose of bringing to the attention of the Live Stock Exchanges and Stockyard Companies the great need of educational and promotional activities in each market territory. Funds were subscribed and Livestock Commissioners employed as follows: W. A. Peck, South St. Paul, Minnesota; Dr. W. T. Spencer, Omaha, Nebraska; R. L. Cuff, Kansas City, Missouri; H. J. Boyts, Sioux City, Iowa; Dr. J. I. Gibson, St. Joseph, Missouri; Dr. D. F. Luckey, St. Louis, Missouri; and Dr. A. J. Knilans, Milwaukee, Wisconsin. H. R. Davison, now Vice-President of the American Meat Institute, assisted at Chicago and all our educational work was coördinated through the Chicago office.

The participation of these leading markets and interior packing companies greatly enlarged the scope of educational work to push forward the campaign of tuberculosis eradication in coöperation with Federal, state and county agencies.

Sentiment favorable for county area testing was accomplished through newspaper publicity, meetings with farmers and local civic organizations. The aid of individual farmers was obtained in circulating petitions to secure the signatures of at least a majority of the cattle owners. Some of the states required the names of considerably more than half the farmers in the county on the petitions. After the necessary signatures were obtained, it was necessary for the Live Stock Commissioners to appear before the County Boards to convince them of the desirability of making a county appropriation to supplement Federal and state funds. Later, the testing of all breeding and dairy cattle in the county was done by Federal, state and local veterinarians under the direction of the U. S. Bureau of Animal Industry, and the state.

On July 23, 1923, the first group of counties was officially accredited by the U. S. Department of Agriculture and the states coöperating. There were 17 in number, located in Michigan, Indiana, North Carolina and Tennessee. During this period, a number of states enacted legislation making provision for the testing of all herds under the county area plan, and appropriations were increased to make this possible. In most of the states this legislation made the circulation of petitions in the county a requirement. Except in one or two states, the county appropriation for the expense of applying the test was made contingent

upon securing the names of at least a majority of the cattle owners on the petitions. In a number of the states, the county appropriations were based on the cattle population at an estimated expense of 25 cents per head.

INCREASED VALUE OF DAIRY CATTLE FROM ACCREDITED COUNTIES

The county area testing in Michigan, Wisconsin, Ohio and Indiana was stimulated through the preference given by eastern buyers to cows produced in accredited counties. The high percentage of reactors found in the eastern states necessitated the purchase of cows from the more western states for replacement purposes. Naturally, the officials of the eastern states made certain regulations to keep out cattle from questionable sections. In consequence, dealers paid a premium for dairy cattle from accredited counties which added greatly to the proceeds from the sale of accredited county cattle.

OPPOSITION

All during the early years of the campaign there was much opposition to the tuberculin test in many communities which had to be overcome. Because the disease rarely reveals itself by external physical symptoms, many refused to believe that their cattle were infected. The accuracy of the tuberculin test was questioned. Some said the injection of tuberculin caused abortions and lessened the milk flow, which of course was erroneous. One of the most convincing things was for a cattle owner to visit the packing plant to see his cattle after slaughter. While the testing was voluntary at first, many states made it compulsory after a large majority requested it. This was necessary to make it complete in every county.

We all stressed the importance of the program from the human health aspects, quoting such authorities as Dr. C. H. Mayo, Dr. D. C. Lochead of the Rochester Minnesota Health Board; Dr. M. J. Rosenau of the Harvard Medical College; Dr. J. A. Myers, University of Minnesota; Dr. Herman N. Bundeson of the Chicago Board of Health, and many others.

All counties in North Carolina were officially declared modified accredited areas in 1928. The infection was light in that state, a few counties revealing no reactors whatever. All counties in Maine were accredited in 1929. Only the southernmost counties in that state were badly infected, the northern portion being of rugged character with the cattle population mostly natives. Michigan, the first dairy state, had all counties officially accredited in 1930, Indiana in 1931, Ohio, Wisconsin, Idaho and North Dakota in 1932, Nevada, New Hampshire and Utah in 1933, Kentucky, West Virginia and Washington in 1934, Illinois, Minnesota, Missouri, Virginia, Kansas, Arkansas, Oregon and Florida in 1935, New Mexico, Louisiana, Delaware, Colorado, Georgia, Arizona, Wyoming, Alabama, Mississippi, Tennessee, Iowa, Texas, South Carolina, Montana, Connecticut, Massachusetts, Oklahoma and Nebraska in 1936, Rhode Island, Pennsylvania, Vermont and Maryland in 1937, and New Jersey, New York and South Dakota in 1938. In 1940 California was the last state in the Union to be officially accredited.

California had a slow start because in the early years of the campaign it was not thought legal to pay indemnity in that state. It was only after the Supreme Court of California ruled that it was legal that real progress was made. Furthermore, many of the counties in California were badly infected. A large number of dairy herds there are owned by Portuguese farmers who perfected a state organization and engaged attorneys to fight the test. This had to be overcome largely by educational means and persuasion.

In this connection it should be explained that the application of the tuberculin test continues after a county is officially accredited, which takes place when, on the last test, less than 0.5 per cent of the cattle react. After accreditation, some counties are tested once in three years, but the quarantined infected herds are tested oftener.

There was a tendency on the part of some County Boards to discontinue appropriations after the county was officially accredited. Accompanied by Dr. A. J. DeFosset, in charge of Federal work of tuberculin testing in Ohio, we visited all of the large cities in that state, appearing before the City Health Boards to present arguments in favor of having ordinances requiring that not only milk but butter also should come from tuberculin tested herds. Previously, a large number of City Health Boards, Baltimore and Chicago being the first, passed ordinances requiring that milk must come from tested herds free from tuberculosis. These regulations did not include butter. It was shown by quoting from government bulletins that the danger from butter was as great as from milk from untested herds. Charts were prepared to show that a sufficient supply of butter was available from tuberculosis-free accredited counties to meet the requirements of the city, and it was no longer necessary to accept butter from nonaccredited counties. The City Health Boards of Cleveland, Columbus, Cincinnati, Dayton, Akron and Canton passed ordinances to require butter to come from accredited counties only. The packages of butter were labeled *Made of Cream from Tuberculin Tested Herds in Officially Accredited Areas.* Any creamery using this label without meeting the requirements was liable to a fine under the Pure Food Laws. Chicago and many other cities adopted similar regulations. These caused the County Boards of Supervisors to continue the appropriations after a county was accredited, or they would lose their status as an accredited county and would then not be able to market their butter in such cities.

The thoroughness of the work of Federal, state and local veterinarians and the capable direction of this work was largely responsible for the success of the whole campaign. We were most fortunate in having Dr. John R. Mohler, a noted scientist and capable executive, Chief of the U. S. Bureau of Animal Industry from 1917 until his retirement one year ago. He was ably assisted by Dr. J. A. Kiernan who died December 13, 1927. His assistant, Dr. A. E. Wight, succeeded him as Chief of Tuberculosis Eradication and has the full confidence of both Federal and state officials throughout the nation.

Inasmuch as all veterinary colleges have well trained faculties, good equipment and thorough courses of study, we were fortunate in having a large number of

well trained local veterinarians who were called upon to assist in the application of the tuberculin test. Now, many of these men are in the service, but with the more limited amount of testing at this time, it has not interfered seriously with the reaccreditation of counties.

Table 1 shows in column 4 the great increase in the number tested each year, in column 5 the number of reactors slaughtered, column 6 the percentage of breeding cattle reacting, column 7 the percentage of all cattle slaughtered under Federal inspection retained for tuberculosis. Columns 2 and 3 show the decline in the human death rate in which the cattle testing was a contributing factor.

AVIAN TUBERCULOSIS

Table 2 shows that the testing of breeding and dairy cattle, the slaughter of the reactors and the disinfection of premises have almost completely eliminated this disease from all cattle, as indicated by the low percentage retained, sterilized and condemned for this disease in 1943. It will be observed, however, that 7 per cent of all hogs slaughtered under Federal inspection in the United States during 1943 were retained for this disease, and a considerable number condemned, practically all of which is of the avian type due to the common practice of permitting hogs to mingle with poultry on our farms. In the twelve north-central states approximately 50 per cent of the poultry flocks are infected with tuberculosis to some degree. The percentage of hogs retained, which is indicative of the prevalence of tuberculosis in poultry, is highest in the most northern states of this central group—Michigan, northwest Ohio, northern Indiana, northern Illinois, Wisconsin, Minnesota, the eastern part of the Dakotas and northern Iowa. In those states over 11 per cent of the hogs slaughtered under federal inspection in 1943 were retained for tuberculosis.

With the limited number of veterinarians it is impossible to apply the tuberculin test to more than the breeding flocks which constitute not to exceed 10 per cent of the total. We are urging all owners who have flocks producing eggs for food purposes only to dispose of them at the end of the first laying year as pullets have little tuberculosis as compared with the older birds and produce 30 per cent more eggs. This has been the practice in the eastern states for many years because of greater economy in young birds, which explains why there is so little tuberculosis in poultry and swine in that area. The same is true in the west coast states. There has never been much tuberculosis in either cattle or poultry in the south.

While avian tuberculosis is readily communicated to swine, it is almost never communicated from poultry to cattle, but, in close contact, infected poultry may sensitize cattle and cause them to react, but such cattle show no lesions.

To what extent avian tuberculosis is communicated to people, we do not know. Dr. L. Van Es, Animal Pathologist, University of Nebraska, tells me that there are 14 authentic cases reported from European sources. It is not believed that avian tuberculosis is readily communicated to people because the disease is so prevalent in the poultry of the north-central group of states that, if it were, the incidence in people would be higher than it is.

TABLE 1

Decrease in the human death rate from tuberculosis in relation to the decrease of this disease in cattle in the United States

The second column shows a gradual decrease in the human death rate per 100,000 population from respiratory tuberculosis. The third column shows a slight increase in the death rate from glandular, bone and abdominal tuberculosis from 1900 to 1917—much of which was of bovine origin—probably the result of the increase in tuberculosis among cattle during that period. Since 1917, with the gradual removal of nearly all tuberculous cattle, there has been a consistent decrease in this death rate from 22.5 to 3.5 (84 per cent) as compared with a decrease of 68 per cent in the death rate from respiratory tuberculosis during the same period. Note similarity in decrease of death rate from nonrespiratory tuberculosis with the decrease in percentage of breeding cattle reacting (92 per cent) and the decrease in percentage of all cattle, exclusive of reactors, retained for tuberculosis (lesions found on postmortem) that were slaughtered under Federal inspection (last column). Data furnished by the U. S. Bureau of Animal Industry and the Division of Vital Statistics, Bureau of Census.

1	DEATH RATES FOR		4	5	6	7
CALENDAR YEAR	2 Respiratory tuberculosis	3 Other forms	CATTLE TESTED FISCAL YEAR ENDED JUNE 30	NUMBER REACTORS SLAUGHTERED	PER CENT BREEDING CATTLE REACTING	PER CENT SLAUGHTER CATTLE RETAINED
1900	180.5	21.4				
1902	162.6	21.9				
1904	176.2	24.5				
1906	155.6	24.6				
1908	144.0	23.6				.88
1909	137.7	23.4				1.27
1910	136.0	24.3				1.42
1911	132.7	26.5				1.57
1912	125.0	24.7				1.98
1913	123.0	24.8				2.02
1914	123.5	23.7				1.98
1915	123.5	22.8				2.11
1916	119.9	22.2				2.35
1917	124.6	22.5	20,101	645	3.2	2.11
1918	128.6	21.4	134,143	6,544	4.9	1.80
1919	107.5	18.1	329,878	13,528	4.1	1.57
1920	97.0	17.0	700,670	28,709	4.1	1.62
1921	85.6	13.3	1,366,358	53,768	3.9	1.62
1922	84.3	12.1	2,384,236	82,569	3.5	1.76
1923	81.3	11.5	3,460,849	113,844	3.3	1.75
1924	78.0	11.7	5,312,364	171,559	3.2	1.56
1925	75.9	10.8	7,000,028	214,491	3.1	1.51
1926	76.6	10.7	8,650,780	323,084	3.7	1.41
1927	71.4	9.5	9,700,176	285,361	2.9	1.15
1928	70.3	9.0	11,281,490	262,113	2.3	1.04
1929	67.6	8.4	11,683,720	206,764	1.8	1.00
1930	63.4	8.1	12,845,871	216,932	1.7	.75
1931	60.7	7.5	13,782,273	203,778	1.5	.62
1932	56.4	6.5	13,443,557	254,785	1.9	.49
1933	53.6	5.9	13,073,894	255,096	2.0	.42
1934	51.2	5.4	15,119,763	232,368	1.5	.36
1935	49.8	5.1	25,237,532	376,623	1.5	.24
1936	50.6	5.0	22,918,038	165,496	.7	.18
1937	49.0	4.6	13,750,308	94,104	.7	.14
1938	48.9	4.3	14,108,871	89,359	.6	.11
1939	42.6	3.9	11,186,805	60,338	.5	.10
1940	41.6	3.7	12,222,318	56,343	.4	.08
1941	40.8	3.7	12,229,499	40,702	.3	.07
1942	39.6	3.5	10,983,086	28,008	.26	.061
1943			9,308,936	17,167	.18	.048

TABLE 2

Decrease in losses from tuberculosis in cattle and hogs

Table showing the number of cattle, exclusive of reactors, slaughtered under Federal inspection, the number and percentage retained, and the number and percentage of entire carcasses sterilized and condemned for tuberculosis.

Compiled from records of the United States Division of Meat Inspection

FISCAL YEAR ENDED JUNE 30	NUMBER SLAUGHTERED	NUMBER RETAINED	PER CENT RETAINED	NUMBER STERILIZED	PER CENT STERILIZED	NUMBER CONDEMNED	PER CENT CONDEMNED	PER CENT STERILIZED AND CONDEMNED
United States cattle (all markets)								
1917	9,276,049	195,488	2.10	8,468	.08	40,746	.43	.51
1920	9,666,188	157,016	1.62	8,610	.08	30,695	.31	.39
1927	9,810,797	112,924	1.15	4,342	.04	27,413	.28	.32
1930	8,119,760	61,192	.75	2,772	.03	12,715	.15	.18
1933	7,554,258	31,971	.42	1,563	.02	6,430	.08	.10
1936	10,215,227	19,076	.18	829	.008	4,027	.039	.047
1939	9,515,754	10,090	.10	403	.004	1,992	.020	.024
1941	10,102,594	8,029	.07	284	.002	1,584	.015	.017
1942	11,743,465	7,255	.061	272	.002	1,593	.013	.015
1943	11,559,167	5,636	.048	198	.001	1,248	.010	.011
Chicago cattle (all plants)								
1917	2,160,899	93,896	4.34	4,757	.22	20,293	.94	1.16
1920	2,155,913	72,551	3.36	4,805	.22	13,937	.65	.87
1927	2,079,362	50,375	2.42	1,592	.07	12,435	.60	.67
1930	1,535,099	17,820	1.16	758	.05	4,388	.29	.34
1933	1,344,373	5,181	.39	287	.02	1,031	.08	.10
1936	1,467,408	2,001	.13	144	.009	538	.036	.045
1939	1,306,526	921	.07	52	.004	253	.019	.023
1941	1,397,595	751	.05	18	.001	209	.014	.015
1942	1,571,659	566	.036	21	.001	163	.010	.011
1943	1,363,566	454	.033	21	.001	159	.011	.012
United States hogs (all markets)								
1917	40,210,847	3,978,168	9.89	91,543	.22	76,807	.19	.41
1920	38,981,914	4,260,719	10.92	94,264	.24	65,609	.17	.41
1927	42,650,443	5,777,708	13.54	73,232	.17	59,656	.14	.31
1930	46,688,860	5,321,352	11.39	53,783	.11	42,381	.09	.20
1933	45,698,053	4,820,152	10.54	40,769	.09	35,680	.07	.16
1936	28,506,019	2,925,593	10.26	16,389	.05	15,195	.05	.10
1939	38,656,537	3,418,805	8.84	15,160	.039	13,190	.034	.073
1941	48,710,059	4,014,021	8.24	15,907	.032	15,317	.031	.064
1942	50,133,871	3,991,367	7.96	14,447	.028	13,357	.026	.054
1943	56,867,080	4,030,207	7.08	13,660	.024	13,051	.022	.046
Chicago hogs (all plants)								
1917	7,550,530	1,229,297	16.28	51,274	.41	25,791	.34	.75
1920	6,772,692	1,018,632	15.04	34,825	.51	18,076	.26	.77
1927	5,655,764	910,463	16.09	15,024	.26	14,850	.26	.52
1930	6,964,441	895,500	12.85	13,038	.18	11,073	.16	.34
1933	6,269,045	671,277	10.70	7,478	.12	6,584	.10	.22
1936	3,481,236	395,315	11.35	2,845	.08	2,506	.07	.15
1939	4,345,549	390,898	8.99	2,131	.04	2,186	.05	.09
1941	5,339,433	424,148	7.94	1,928	.036	2,589	.048	.084
1942	5,066,766	358,154	7.06	1,410	.027	2,038	.040	.067
1943	5,732,018	363,690	6.34	1,210	.021	1,950	.034	.055

FEWER HUNCHBACKS TO-DAY

As a matter of common observation, there are to be seen to-day relatively few hunchbacks on our streets as compared with twenty-five years ago, which is doubtless explained in part by the results of the cattle campaign. Under date of April 26, 1944, Dr. J. A. Myers, Professor of Preventive Medicine, University of Minnesota, and author of the book *Man's Greatest Victory over Tuberculosis*, writes:

"The statement concerning hunchbacks was that many of them were caused by bovine tubercle bacilli. In England, as I recall, Dr. Stanley Griffith found by typing the organisms that about 25 per cent of all cases of bone and joint tuberculosis were caused by the bovine tubercle bacillus. I have often wondered if the percentage were not higher in this country because the disease of the bones and joints has decreased so rapidly and apparently parallel with the control of tuberculosis among cattle. However, I do not know of any figures or any report where typing was actually done.

"I am strongly of the belief that the rapid decline in tuberculosis in this country during the last two decades has been due in no small part to the control of bovine tuberculosis. I believe this applies to the mortality, morbidity, and certainly to the infection attack rate. The decrease in the incidence of tuberculin reactors among children has been phenomenal; in fact, we now have whole counties where not more than 5 to 8 per cent of the senior students in high school react to the tuberculin test.

"Dr. L. S. Jordan, Superintendent of Riverview Sanatorium, at Granite Falls, Minnesota, has recently sent me some results of testing in schools over a period of ten years, and in some of these schools there is no longer a single reactor to tuberculin whereas ten years ago the percentage of reactors was ten or more. You may know that Dr. Jordan has been an enthusiast for tuberculosis control among animals, and he has left no stone unturned to assist those in the animal tuberculosis program."

The success of the entire campaign has been due entirely to the fine coöperation of all branches of the livestock industry, agricultural associations, livestock organizations, civic clubs and medical groups.

It is not unreasonable to think that, in the future, all people will be tuberculin tested and X-rayed, under the county area plan, the reactors isolated and given modern successful medical treatment. As you all know, many universities, high schools, grade schools, industrial organizations and certain communities have already conducted tuberculin tests or made use of X-ray films, and it is greatly to be hoped that this will continue to expand.

SUMMARY

The cattle in the United States first became infected with tuberculosis from importations of breeding cattle from Europe, long before we had the tuberculin test. The disease spread until, in 1916, of all cattle slaughtered under Federal inspection in the United States 2.35 per cent were retained for tuberculosis (lesions found on postmortem examination), the percentage infected being much higher.

It was transmitted from cattle to swine through infected milk and droppings. In 1917, 40,746 cattle and 76,807 hogs were condemned for tuberculosis and

tanked as inedible under Federal inspection, enough to fill a stock train twenty-two miles long. It was then that an educational campaign was started at Chicago with funds subscribed by market interests to promote a national campaign of eradication, followed later by other western markets.

Appropriations were made by Congress, state legislatures, and county boards which were increased each year until 1935 when all totaled $26,792,179 for both indemnity and operating expense.

County area testing was started in 1921. The first 17 counties were officially accredited as being practically free from bovine tuberculosis in 1923, and all counties in the United States by 1940.

Many packing companies paid a premium of 10 cents per hundred on hogs produced in accredited counties, which aided materially. Much opposition by farmers to the project was overcome by stressing its importance as a public health measure.

In 1943 the incidence of the disease in all cattle had been reduced 98 per cent, but in hogs much less because of the prevalence of tuberculosis in poultry (avian) which is readily communicated to hogs, but rarely to cattle.

Since 1917 there has been a decrease of 68 per cent in the human death rate from respiratory tuberculosis and 84 per cent in other forms, to a considerable extent the result of eliminating the disease in cattle.

SUMARIO

El ganado vacuno de los Estados Unidos se infectó primeramente con tuberculosis por animales de cría importados de Europa mucho antes de introducirse la reacción a la tuberculina. La enfermedad continuó propagándose hasta que en 1916, de todos los animales degollados bajo inspección federal en el país, 2.35% fueron decomisados por tuberculosis (lesiones descubiertas en el examen autópsico), aunque el porcentaje infectado era mucho mayor.

Del ganado vacuno la enfermedad se trasmitió a los cerdos por medio de la leche y excrementos infectados. En 1917, 40,746 bovinos y 76,807 cerdos fueron decomisados por tuberculosis y destruídos como impropios para consumo bajo la inspección federal, o sea una cantidad suficiente para llenar un tren de ganado que ocuparía unos 40 km de espacio. Fué entonces que con fondos suscritos por intereses comerciales de Chicago, se inició una campaña educativa con miras a una campaña nacional de erradicación en que participaron después otros mercados del oeste del país.

El Congreso nacional, las legislaturas de los estados y las juntas de los condados del país facilitaron fondos que aumentaron cada año hasta alcanzar el 1935 la suma total de $26,792,179 destinada a cubrir tanto los gastos de indemnización como los de administración.

La comprobación del ganado fué iniciada en 1921 y para 1923 ya se pudieron considerar prácticamente exentos de tuberculosis bovina los primeros 17 condados y todos los condados del país para 1940.

Muchas compañías frigoríficas pagaban una primera de 10 centavos por cada 100 libras de carne de cerdo producida en condados "certificados", lo cual ayudó

decididamente en la campaña. La oposición de los labradores al plan fué vencida haciendo resaltar la importancia de la misma como medida sanitaria.

Para 1943 la frecuencia de la enfermedad en todo el ganado vacuno había sido reducida en 98%, pero mucho menos en los cerdos debido a la difusión de la tuberculosis en las aves de corral (forma aviaria), que se trasmite fácilmente a los cerdos pero rara vez a los bovinos.

Desde 1917 ha habido una disminución de 68% en la mortalidad humana debida a la tuberculosis pulmonar, y de 84% en las otras formas, debido esto en gran parte a la eliminación de la enfermedad en el ganado bovino.

SPECIFIC METABOLIC PRODUCTS OF THE TUBERCLE BACILLUS[1,2]

An Unsuccessful Search for Them in the Urine of Tuberculous Patients

JOHN T. RIORDAN

The present investigation was undertaken with the object of attempting to demonstrate specific fractions of the tubercle bacillus in urine from patients with pulmonary tuberculosis. This is based on the presence in the urine of antigens derived from the incitant in other diseases, notably pneumococcus pneumonia (1), scarlet fever (2) and trichinosis (3). In view of the great divergence of opinion as to the presence of urinary antigens in tuberculosis, it was felt that the detection of known chemical fractions of the tubercle bacillus by serological methods would be more convincing proof of their presence than the evidence elicited by a skin reaction, such as the Wildbolz auto-urine test (4, 5, 6, 7, 8). In the Wildbolz test, which seemed to indicate that a tuberculin-like substance was excreted during active tuberculosis, 0.05 ml. of the patient's concentrated urine is injected intracutaneously and the reaction produced is read in a manner similar to the usual tuberculin reaction. As the intracutaneous skin test with urine is apt to give rise to nonspecific inflammation, the difficulties of controlling and interpreting such a reaction are obvious. In view of the successful detection of the specific pneumococcus polysaccharide in the urine of pneumonia patients by Dochez and Avery (1), and because of other considerations, our first efforts were concentrated on an attempt to demonstrate the polysaccharide fraction of the tubercle bacillus in the urine of tuberculous patients.

Polysaccharide

The chemical and biological properties of tubercle-bacillus polysaccharide have been investigated by many workers. Zinnser (9), in 1921, isolated a substance from tubercle-bacillus extracts which gave precipitin reactions with specific sera and also produced skin reactions in tuberculous animals. This substance, which he called "residue-antigens," was precipitated by alcohol and resisted heat. Later studies showed that the skin-reactive component was an impurity and the "residue-antigen" was in reality a crude polysaccharide.

Laidlaw and Dudley (10), in 1925, isolated a gum from human tubercle bacilli, which gave precipitin reactions with immune serum but did not induce antibody formation.

Mueller (11), working with a tuberculin produced by growing the H37 strain of tubercle bacillus on a synthetic medium, isolated a gum which gave precipitin reactions in high dilutions with immune serum. The hydrolyzed solution yielded reducing substances equivalent to 99 per cent glucose.

Anderson (12), in 1927, isolated a polysaccharide from the aqueous-alcohol

[1] From the Section of Preventive Medicine, Yale University School of Medicine, New Haven, Connecticut.

[2] Aided by a grant from the National Tuberculosis Association.

fraction that remained after tubercle bacilli had been extracted with ether and alcohol. Anderson (13) also obtained a polysaccharide from the bound lipids and wax fractions of the human tubercle bacillus.

Masucci, McAlpine and Glenn (14) isolated a polysaccharide complex of the nature of a gum from the filtrate of tubercle-bacillus cultures grown on synthetic medium. This polysaccharide gave a precipitate, in high dilutions, with immune sera produced by injecting animals with the microörganisms; but did not react with sera produced by injecting animals with the filtrate from cultures. It failed to elicit a skin reaction in tuberculous patients or in tuberculous guinea pigs. Later studies by the same authors (15) showed that, with the H37 strain of tubercle bacilli, "the maximum amount of reducing substances before and after hydrolysis appeared in the filtrate between the seventh and ninth week of growth. Likewise, the precipitin titre jumped very markedly during the seventh week and kept gradually increasing until the sixteenth week."

Our own studies, as well as those of others, have shown that minute quantities of the polysaccharide fraction of the tubercle bacillus, less than 1 part per million, can be measured by means of precipitin reactions and collodion-particle agglutinative tests with immune serum (16). It has also been shown that polysaccharide could be detected in infected material from patients and animals, only when the tubercle bacilli present were artificially disintegrated (17). It would seem likely, nevertheless, that during the course of tuberculosis some bacilli do disintegrate and that polysaccharide and/or other fractions of the tubercle bacillus might be set free within the lesion and eventually be excreted in the urine. The experiments described below were set up with this in view.

MATERIALS

Immune serum: Anti-H37 tubercle-bacillus serum 5807 was used for the detection of polysaccharide. It was prepared by the Mulford Biological Laboratories of Sharp and Dohme in 1925 by the injection of a horse with defatted tubercle

TABLE 1

Urines tested for tubercle-bacillus polysaccharide

STAGE OF DISEASE	FAR ADVANCED	MODERATELY ADVANCED	MINIMAL	ARRESTED	TOTAL
Number of patients	37	28	18	6	89
Number of urines	85	60	45	20	210

bacilli. The immunological properties of this serum have been studied by a number of investigators (18), including Heidelberger (19), who found its antibody content to be almost entirely of antipolysaccharide specificity. This was confirmed in our own tests in a previous study (16).

Urine: Two hundred and ten specimens from 89 patients with pulmonary tuberculosis were used as a possible source of polysaccharide-containing material (table 1). Twenty-two urines were also collected from 8 tuberculous rhesus

monkeys (*M. mulatta*). All urines were collected in chemically clean bottles with a small amount of toluol added as a preservative.

SEROLOGICAL METHODS FOR DETECTING ANTIGENS

(*1*) *Precipitin reactions* were set up in tubes with an inside diameter of 4 mm., using 0.2 ml. of antigen and 0.2 ml. of anti-H37 tubercle-bacillus serum. They were left in the incubator for two hours at 37°C. and then kept in the ice-box until read at the end of twenty-four and forty-eight hours. All antigens were set up with normal horse serum controls. Dilutions of antigen up to 10^{-2} were also tested.

(*2*) *Collodion-particle agglutination:* The principles underlying this technique have been laid down by Freund (20) and Cannon and Marshall (21) and developed by Goodner (22). Tests were set up in standard agglutination tubes with 0.5 ml. antigen, 0.1 ml. collodion particle suspension, 0.1 ml. anti-H37 tubercle-bacillus serum and 0.3 ml. saline. The suspension was added before the antigen and antibody were allowed to combine. The tubes were incubated at 37°C. for two hours and then kept in the ice-box overnight. They were then centrifuged at 1400 RPM for five minutes and read. All antigens were set up with normal horse serum controls. Dilutions of antigen up to 10^{-2} were also tested.

URINE CONCENTRATION AND PRECIPITATION

Four methods were used:

(*1*) *Heat in vacuo:* A twenty-four-hour sample of urine was filtered through paper on a Buchner funnel and the filtrate collected in a vacuum flask. It was then concentrated at 50° to 55°C. under reduced pressure to about 75 ml. and cooled in the ice-box for two hours. The concentrated urine was filtered through paper and the residue washed with a small amount of distilled water. The filtrate was placed in a cellophane bag[3] and dialyzed against running tap water for eight to twelve hours in order to reduce the salt content. The dialysate was then concentrated under reduced pressure to dryness and taken up in normal saline. This solution was centrifuged and the supernatant used. Sixty-two urines were concentrated by this method and tested.

(*2*) *Pervaporation:* McAlpine and Masucci (23), using a human type tubercle-bacillus polysaccharide, found that during mild acid hydrolysis the destruction of its precipitinogenic capacity proceeds at a much greater rate than the cleavage of the polysaccharide into simple sugars. From an original precipitin titre of 1,500,000, they found the titre dropped to 640,000 after two hours' hydrolysis with N/25 sulfuric acid at 100°C. and to 40,000 after six hours. In view of their findings, we felt that concentration of urine at temperatures lower than that used (50° to 55°C.) might overcome any slight chance of loss of biological activity of the polysaccharide, if present in the urine. The following method was used:

A twenty-four-hour sample of urine was filtered through paper on a Buchner

[3] The cellophane used in these experiments is known as Visking casing.

funnel and the filtrate was put in cellophane bags. The ends of the bags were then strung horizontally to tension springs between two large circular wooden discs which were rotated by a motor. A heating coil in the bottom of the unit was used as a source of infra-red rays to aid in pervaporation and the air current from two electric fans was directed towards the rotating bags. By this method, concentration of the urine was carried out at a temperature below that of room temperature. When the twenty-four-hour urine specimen was concentrated to approximately 100 ml., the cellophane bags were immersed in running tap water and dialyzed for eight to twelve hours. The dialysate was again pervaporated to a small volume, centrifuged and the supernatant used. Seventy-six urines were concentrated by this method and tested.

In these two methods, dialysis of the concentrated urine was necessary to remove the urinary salts and other substances that give nonspecific reactions with both normal and immune horse serum. As the tubercle-bacillus polysaccharide molecule is known to be partially dialyzable through cellophane membranes, positive controls were run to estimate the loss. Positive precipitin reactions were encountered in dilutions of polysaccharide as high as 1 part in 1,600,000 before dialysis but, when polysaccharide was added to large volumes of urine, concentrated as above and dialyzed through cellophane for the minimum period necessary to remove nonspecific factors, it was found that the precipitin titre dropped to 1 part per million. Longer dialysis resulted in a much greater loss.

(*3*) *Alcohol precipitation:* Because of the possibility of losing some polysaccharide by dialysis and in view of the insolubility of polysaccharide in ether and alcohol, the following methods were also used. Five hundred ml. of urine was extracted with ether and allowed to stand overnight. The next morning the clear layer of underlying urine was drawn off and concentrated either by pervaporation or under reduced pressure to about 50 ml. It was cooled in the ice-box for two hours, centrifuged and the supernatant again concentrated to a thick syrup. The syrup was triturated with absolute alcohol until a coarse powder was produced. The powder was washed with absolute alcohol and dried in a vacuum desiccator. It was then dissolved in water, centrifuged and the supernatant used. Fourty-six urines were concentrated and precipitated by this method and tested.

(*4*) *Lead acetate precipitation:* Twenty-four-hour urine specimens from active cases of far advanced tuberculosis were pooled to obtain 10 litres of urine. The urine was extracted with ether and allowed to stand overnight. The clear layer of urine was drawn off and a concentrated solution of neutral lead acetate was added until no further precipitate was produced. The resulting copious precipitate was filtered off on a Buchner funnel and washed with a small amount of distilled water. The filtrate was concentrated under reduced pressure to a thick syrup, filtered on a Buchner funnel and washed with a little water. The solution was mixed with 25 per cent basic lead acetate and made strongly alkaline with ammonium hydroxide. This mixture was allowed to stand at room temperature for a few hours and the precipitate which formed was filtered off and

washed with dilute ammonia. After most of the ammonia had been removed by standing in a vacuum desiccator over sulfuric acid, the still moist precipitate was rubbed into a suspension in water and decomposed with hydrogen sulfide. The lead sulfate was filtered off and washed with water. The clear filtrate was concentrated under reduced pressure to near dryness. The material was triturated with absolute alcohol until a coarse powder was produced. The powder was filtered off, washed several times with absolute alcohol and dried in a vacuum desiccator. It was dissolved in distilled water, centrifuged and the supernatant used for tests. Twenty-six urines were used to form 3 pools which were precipitated as described above and tested.

POSITIVE CONTROLS

When a fraction of a milligram of polysaccharide was added to urine it could be readily detected in high dilutions (1 part per million) by the methods outlined above. Polysaccharide solution, left in contact with tuberculous and nontuberculous tissue at 37°C. for one week, also gave positive precipitin reactions in high dilutions (1 part in 1,200,000) when tested with immune serum. Intravenous injections of polysaccharide solution into 2 tuberculous and 2 nontuberculous rhesus monkeys were done in an attempt to determine the effect of living tissue on tubercle-bacillus polysaccharide. These monkeys were placed in metabolism cages and the urine was collected over a period of seventy-two hours. Following concentration by heat *in vacuo*, polysaccharide could be detected in high dilutions in the urine from all 4 monkeys.

Wallace and Bray (24), in an investigation of the action of bacterial enzymes on the carbohydrates of the tubercle bacillus, found by chemical methods that *L. pentoaceticus* and *B. macerans* destroyed the carbohydrates whether in the form of the hydrolysate, or present in dead or in living virulent bacilli. No tests were done to determine the rate of destruction of serological activity. Although toluol was added as a preservative in the collection of urines for our experiments, it was thought worth while to investigate the effect of bacteria present in urine on polysaccharide. A solution representing 0.1 mg. of tubercle-bacillus polysaccharide was added to urine specimens, without toluol, and they were allowed to stand at room temperature for varying periods of time. These urines were then concentrated at intervals of one, two, three, four, and six days. Precipitin tests with immune serum showed that the polysaccharide could be readily detected in these urines. From the results of this small series of tests, it was felt that, for our purposes, bacteria normally present in urine exert no deleterious effect on the precipitin power of tubercle-bacillus polysaccharide.

RESULTS OF POLYSACCHARIDE EXPERIMENT

All tests for polysaccharide in urine, from patients in any stage of tuberculosis, gave negative results with the methods described. In 2 separate instances, positive results were encountered in low dilutions with concentrated urine from rhesus monkeys with far advanced generalized tuberculosis. It was noticed, however, that particles of stool were present in the urine specimens collected from

these monkeys and, upon examination by direct smear, these stools were found to contain large numbers of acid-fast bacilli. As noted in a previous communication (17), positive reactions may be encountered in low dilutions in material in which acid-fast bacilli are present, if sufficient bacilli are lysed or disintegrated in any one of several ways. Specially prepared, Seitz-filtered extracts of these monkey stools also gave precipitin reactions when acid-fast bacilli were present in large numbers. Therefore, these 2 positive reactions in monkey urine were not considered conclusive.

After our failure to detect polysaccharide in the urine, it was felt that the possibility of serological detection of other antigenic fractions of the tubercle bacillus, namely, phosphatide and protein, was slight. However, such an attempt was made.

TABLE 2

Urines tested for tubercle-bacillus phosphatide

STAGE OF DISEASE	FAR ADVANCED	MODERATELY ADVANCED	MINIMAL	TOTAL
Number of patients	12	8	4	24
Number of urines	28	16	8	52

TABLE 3

Urines tested for tubercle-bacillus protein

STAGE OF DISEASE	FAR ADVANCED	MODERATELY ADVANCED	MINIMAL	TOTAL
Number of patients	10	6	2	18
Number of urines	22	12	4	38

Tuberculophosphatide

In our search for phosphatide, 52 urine specimens from 24 active cases of pulmonary tuberculosis (table 2) were concentrated by pervaporation and extracted with ether. The method employed was that of Anderson's, used by Smithburn and Sabin (25) for the extraction of phosphatide from an aqueous solution. These extracts were used as a possible source of phosphatide containing material. Precipitin reactions, using immune rabbit sera capable of detecting tuberculophosphatide in dilutions of 1 part per 100,000, were in all cases negative.

Tuberculoprotein

Negative results were also encountered in the search for tuberculoprotein in the urine. Thirty-eight urines from 18 active cases of pulmonary tuberculosis (table 3) were concentrated by pervaporation and precipitated with ammonium sulfate (26). Precipitin reactions and collodion-particle agglutinative tests, using immune rabbit sera with a precipitinogenic titre of 1:100,000, gave negative

results with all urines tested. Skin tests of 20 urine extracts in tuberculous rhesus monkeys were also negative. These monkeys had been previously tested with OT 1 mg., and were found positive according to the technique described by Schroeder (27) and Kennard *et al.* (28, 29).

COMMENT

A special polysaccharide is known to be a definite constituent of the tubercle bacillus, having been isolated by Anderson (12) and others (10). This polysaccharide is liberated in synthetic liquid medium when tubercle bacilli are grown for a sufficient period of time, and is probably a product of cell autolysis. In a previous study (17) we were able to demonstrate polysaccharide by serological methods in heavily infected tuberculous tissue only when the tubercle bacilli present in the lesion were artificially lysed or disintegrated. In a paper published since this investigation of urine began, Anderson *et al.* (30) examined tuberculous human lung tissue for certain specific chemical compounds, namely, phthiocol, tuberculostearic acid, phthioic acid and the specific polysaccharide, which occur in the human tubercle bacillus when grown on a synthetic medium. He found it impossible to detect even traces of the specific substances although they could be isolated and identified when incorporated with normal human lung tissue. Our failure to detect polysaccharide in urine might indicate that either polysaccharide is not liberated *in vivo*, as it is in *in vitro* growth of the tubercle bacillus, or that some mechanism exists which destroys or alters the polysaccharide soon after it is liberated. If tubercle bacilli do autolyze or are degenerated in the body during the course of the disease tuberculosis, the amount of polysaccharide excreted in the urine is so small that it cannot be detected by the delicate immunological methods used. Positive controls showed these methods to be adequate to the extent of detecting tubercle-bacillus polysaccharide in urine in dilutions as high as 1 part per million.

Our negative results in the search for phosphatide might be explained by the biological reactions of this fraction when injected intraperitoneally into rabbits. Smithburn and Sabin (31), using a phosphatide isolated by Anderson (32), have shown that it is phagocytized by young connective tissue cells or monocytes. The lipoid is then dispersed into fine particles with the formation of classical epithelioid cells. A similar, though more complex, process occurs when infection with living organisms takes place. Therefore, liberation of phosphatide in the body and excretion of this substance in the urine would seem to be a very slow process, if it did occur. Whatever the explanation may be, only negative results were encountered with the methods used in this experiment.

The failure to demonstrate tuberculoprotein in the urine by serological methods was not surprising. Seibert (33) has shown that the whole tuberculoprotein is a true antigen, capable of inducing antibody formation in rabbits and guinea pigs. It also gives precipitin reactions with such immune sera in high dilutions. However, tuberculoprotein altered by heat or by chemical agents reacts poorly or not at all with immune sera, despite the fact that such protein may be relatively potent in skin reacting properties. Our antiprotein sera would not give precipitin reactions with heat-prepared Old Tuberculin while it reacted with

TPT (tuberculoprotein trichloracetic acid precipitated) in dilutions of 1 part per 100,000. Acid hydrolysis under certain conditions and even prolonged heating in water splits the protein molecule (34). Certain digestive enzymes also change the whole protein molecule to proteose and amino acids with a resultant loss of activity (35). It would be expected that any protein liberated from the tubercle bacillus might be subjected to some such denaturing before being excreted in the urine.

While it is recognized that the skin reactivity to tuberculoprotein is not as delicate in monkeys as it is in humans, significant amounts of this substance should have been detected by the methods used in this experiment.

SUMMARY

1. Specific polysaccharide could not be detected in 210 concentrated urine extracts from 89 patients in various stages of pulmonary tuberculosis by precipitin reactions or collodion-particle agglutinative tests with immune serum.

2. When urine to which polysaccharide had been added was concentrated and tested by the methods described, polysaccharide could be detected in dilutions as high as 1 part per million.

3. The precipitin power of polysaccharide is not destroyed by bacteria normally present in urine during a period of six days' contact at room temperature.

4. Tuberculophosphatide could not be detected in 52 concentrated ether extracts of urine from 24 active cases of tuberculosis by precipitin reactions with immune serum.

5. Tuberculoprotein could not be detected in 38 concentrated and ammonium sulphate precipitated fractions of urine from 18 active cases of tuberculosis by precipitin reactions and collodion-particle agglutinative tests with immune serum.

6. Twenty skin tests in the periorbital region of tuberculous monkeys with ammonium sulfate precipitated fractions of urine were also negative.

SUMARIO

1. En 210 extractos concentrados de orina de 89 enfermos en varios períodos de la tuberculosis pulmonar, no pudieron descubrirse polisacáridos específicos ni por medio de precipitinorreacciones, ni de pruebas aglutinantes con partículas de colodión, en suero inmune.

2. Cuando se concentraba y comprobaba con las técnicas descritas, orina a la que se había agregado algún polisacárido, pudieron descubrirse éstos hasta en diluciones de una parte por millón.

3. El tenor en precipitinas de los polisacáridos no es destruído por las bacterias normalmente presentes en la orina, durante un período de seis días de contacto con la temperatura ambiente.

4. No pudieron descubrirse tuberculofosfátidos en 52 extractos etéreos concentrados de orina procedente de 24 casos activos de tuberculosis, por medio de precipitinorreacciones con suero inmune.

5. Por medio de reacciones de precipitinas y aglutinación con partículas de colodión en suero inmune, no pudo descubrirse tuberculoproteína en 38 fracciones

de orina procedente de 18 casos activos de tuberculosis, concentrada y precipitada con sulfato de amonio.

6. También resultaron negativas 20 cutirreacciones ejecutadas en la región periorbitaria de monos tuberculosos, con fracciones de orina precipitada con sulfato de amonio.

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PROMIN INHALATION THERAPY IN PULMONARY TUBERCULOSIS[1]

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The use of promin (p,p′diaminodiphenylsulfone-N,N′-didextrose sulfonate) in experimental tuberculosis in guinea pigs has met with promising results, both when given orally (1, 2) and when inhaled as a nebulized spray (3). On the other hand, the clinical results, when promin has been administered orally (4, 5), intravenously (6) and locally (7), have been discouraging, except in so far as techniques for further investigation have been developed. Because there appeared to be a possible advantage in combining local topical effect with the effect of general absorption, it was decided to use promin inhalation therapy in a clinical trial.

Preliminary experimental studies[3] on the absorption of sulfonamides when inhaled by animals had already been carried out. These studies consisted in checking blood levels in rabbits, cats, guinea pigs and rats after they had been exposed from fifteen minutes to two hours in a sulfonamide "mist." The "mist" was created by spraying a solution of either sodium sulfathiazole or sodium sulfadiazine into an oxygen tent into which the individually caged animals, with heads exposed, were placed. The sulfonamide solution was sprayed into the tent during the exposure period by means of a home-made glass atomizer corked in a large flask and attached to a motor blower. The blood levels thus obtained ranged from traces up to 8 mg. per cent, depending on the length of exposure. On autopsy, however, some of the animals showed marked hyperaemia of the lungs, and it was therefore decided that the high alkalinity of these drugs contraindicated their use for this type of inhalation treatment. This decision was later confirmed by others (8).

Meanwhile other investigations had been made along this line. For example, it had been demonstrated that the extent of distribution of inhaled dyes in the lungs depended largely on the diameter of the droplets (9), and that fine droplets, smoke or dust particles can penetrate at least into the smaller bronchi (9, 10, 11).

The introduction of adrenalin inhalation therapy for asthma (12) stimulated further interest in this country. The Graeser atomizer used for this treatment produced droplets measuring 2 to 3 micra in diameter. The "mist" produced, however, disappeared too rapidly for deep penetration. It was pointed out that a "mist" with a quality of permanency, suitable for deep inhalation, was dependent on the factors of vapor pressure, nuclei formation and surface tension of the droplets (13). The classical study of germicidal vapors and aerosols (droplets of 1 to 2 micra diameter) threw further light on the subject.

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[3] This preliminary study, as well as the treatment of three of the patients of the series to be described, was developed during three months at City Hospital, New York City. The greater part of the whole study was carried on and completed at the Municipal Sanatorium, Otisville, New York. These institutions are units of the Department of Hospitals of the City of New York.

By this time the foundation had been laid for administering a variety of drugs by means of inhalation. Therefore, with the advent of the sulfonamides and their success in topical application, it was natural to think of using them for inhalations as well as for drops and sprays. Because of its nonalkalinity, prontosil seemed promising in this repsect (15), as did later the microcrystalline suspensions of sulfathiazole (8). Finally the sulfone, promin, having a pH of 5.6 to 6.0 in a 40 per cent solution, seemed ready for investigation of its clinical possibilities when administered by inhalation.

A study of sprays and vaporizers resulted in the selection of an apparatus (previously described (16)) capable of producing a "mist" which was judged by the criteria referred to above to be superior to others for absorption by deep inhalation. Preliminary studies[4] of blood levels, obtainable by different methods

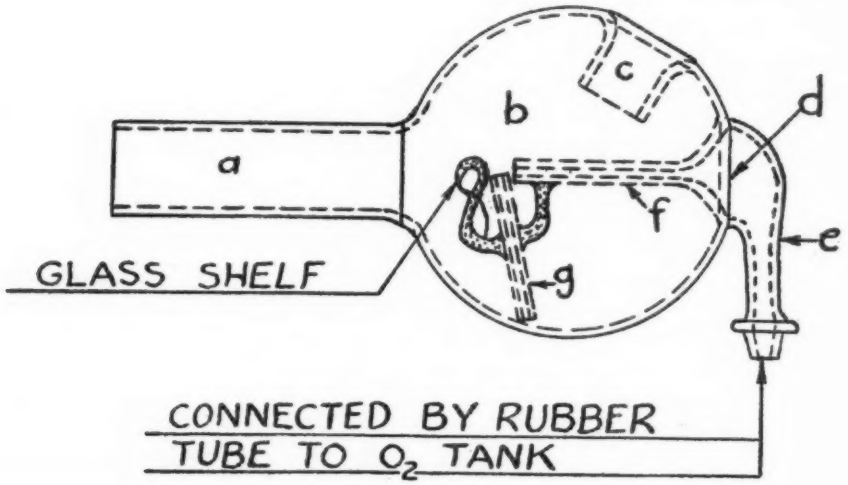

FIG. 1

of inhalation with this apparatus called a vaporizer,[5] were carried out. The method of allowing inhalation of the promin "mist" or liquid vapor, collected in specially designed hoods covering the patients' heads and shoulders, was discarded because wasteful amounts of the drug were necessary to obtain mere traces in the blood. Finally the method of placing the stem of the vaporizer deep in the mouth, with lips closed around it, and teaching the patients to inhale through the vaporizer and exhale through the nose, proved effective in maintaining what were deemed therapeutic blood levels. Figure 1 illustrates the vaporizer.

The glass stem (a), $1\frac{1}{4}''$ long, $\frac{1}{2}''$ wide, is connected with a round central receptacle (b), which has two openings, one on top (c) and one on the side (d). The opening (c) is used for the introduction of the medicinal solution. The opening (d) has a glass extension (e), $1''$ long, shaped so that a rubber tube can be easily

[4] See footnote 3.

[5] Supplied by the Vaponefrin Co., Philadelphia, Pennsylvania.

connected. From the inner side of the opening (d) a hollow horizontal glass stem (f) extends to the middle of the receptacle, where it is connected with a hollow vertical glass stem (g). The solution placed in the receptacle (b) is sucked into the vertical stem (g) at the top of which it is vaporized by a stream of oxygen coming through the horizontal stem (f). The vapor passes out through the main stem (a).

The downward stem (e) was connected to an oxygen tank with a flow of six liters per minute. The promin solution was diluted with an equal quantity of sterile water and placed in the central receptacle. The oxygen under pressure produced a fine promin vapor. A small portion of the vapor was lost through the opening (c) but the major part was inhaled. Each treatment took from ten to fifteen minutes.

The promin[6] was supplied in 2.5 cc. (1 gram) ampules. The dose varied from 1.6 to 3 g. per day, divided into four daily treatments during the first three weeks, and thereafter five daily treatments.

In order to determine the value of promin, patients with various types of lesions were selected for treatment. These lesions were classified as follows:

1: Fresh or exudative.
2: Mixed infiltration or exudative-productive.
3: Tuberculous cavities, recent or old.
4: Bronchiectasis associated with tuberculosis.
5: Tuberculous endobronchial ulcers.

The treatment was given to 24 patients, 11 men and 13 women, of whom 19 were white and 5 colored. Their ages varied from sixteen to fifty, but 75 per cent were under forty. The duration of the treatment varied from two to six months and in 66 per cent of the cases it was administered three months or longer.

The treatment was started with the administration of 1.6 g. daily in four doses. In uncomplicated cases the amount of promin was increased within three weeks to 2 g. daily in five doses, with increases of 0.5 g. each month till a daily dose of 3 g. was administered in five treatments. The 3 g. dose was not exceeded. Only 46 per cent of the patients reached a 3 g. dose. The others did not have the medication long enough to reach this dosage or else there were indications to reduce the daily dose.

The total amount of promin used for each patient varied from a minimum of 58.8 g. to a maximum of 343.2 g. with an average of 196.4 g. for the entire group. There was no direct relationship between the total dosage and the duration of treatment; when there was any evidence of toxicity the dose was not increased.

Every week the following laboratory examinations were made for each patient: promin blood level, haemoglobin, white cell count, differential count, sedimentation rate and urine. The promin blood levels are tabulated in table 1.

The blood levels show important variations without a uniform pattern. Thus

[6] The promin for this study was very generously furnished by Parke, Davis & Company through Dr. E. M. Sharpe, the Director of the Department of Clinical Investigation of the Company.

the total average blood level was 1.07 mg. per 100 cc. of blood, with minimum and maximum averages of .45 mg. to 1.77 mg. Though some of the figures for the minimum blood level agree with the average of .5 mg. for the entire group, there are many individual variations from the minimum of .25 mg. to the maximum of 1 mg. There is some variation also in the maximum blood levels, with an average of 1.79 mg. for all the cases. Minimum and maximum values varied from .5 mg. to 3.5 mg.

An attempt was made, by a progressive increase of the dose of promin, gradually to increase the blood level and maintain it at a certain figure. This was not

TABLE 1

*Promin blood level determinations (mg. per 100 cc. blood)**

	TOTAL DOSAGE IN GRAMS	AVERAGE BLOOD LEVEL IN MG. PER 100 CC.	MINIMUM BLOOD LEVEL IN MG. PER 100 CC.	MAXIMUM BLOOD LEVEL IN MG. PER 100 CC.		TOTAL DOSAGE IN GRAMS	AVERAGE BLOOD LEVEL IN MG. PER 100 CC.	MINIMUM BLOOD LEVEL IN MG. PER 100 CC.	MAXIMUM BLOOD LEVEL IN MG. PER 100 CC.
1	207.6	.45	.25	.5	13	161.4	1.09	.3	2
2	106.6	.61	.25	1	14	156.6	1.17	.25	2.4
3	58.8	1.5	1	2.2	15	289.1	1.18	.25	2
4	161.7	.66	.5	1	16	165.6	1.27	1	2
5	164.1	.68	.5	1	17	259.1	1.29	.35	2
6	244.4	.71	.5	1.2	18	120.6	1.41	.75	2.25
7	175.1	.75	.75	.75	19	261.4	1.42	.7	2
8	253.1	.79	.25	1.5	20	105.6	1.75	1	2.75
9	227.4	.95	.3	1.75	21	190.5	1.77	.5	3.5
10	152.2	1	.5	1.75	22	281.1**	?	?	?
11	101.6	1.05	.25	1.5	23	335.2**	?	?	?
12	241.1	1.05	.5	2.5	24	343.2**	?	?	?

* The average, minimum, and maximum blood levels were derived from the blood determinations where an actual amount of promin could be demonstrated, for there were instances where the blood examinations showed only a trace or no promin at all, with no mathematical figure to be recorded. These determinations were made weekly, except where the administration of the drug was temporarily discontinued for some reason.

** This is as nearly accurate a figure as it is possible to get. These are the three patients previously treated at City Hospital.

possible. There was no uniform blood level pattern, as shown by the many variations in table 1. There were great differences between minimum and maximum levels, not only for the entire group but in individual cases. This change of blood level was a constant feature of most of the cases, although in some a regular level was temporarily obtained. No one case showed the steady maintenance of a uniform blood level and no typical blood curve could be established. Thus there was no direct relationship between the promin dosage and the blood level. However, the majority of cases showed demonstrable blood levels even though the amounts varied and often only a trace was found.

There are many explanations for these blood level differences. In the first place, the promin level in the blood does not persist for long. It has been reported (17) that promin concentration in the blood rapidly declines, and that "only

traces remained in the blood six to eight hours following the intravenous administration of 5 grams of promin."

The actual absorption of the drug also varies greatly. A patient coöperating poorly could vary the absorption by poor application of the lips around the glass stem and by not keeping the vaporizer continually in the mouth. The waste through nasal exhalation and through the upper opening of the vaporizer (c) contributed to a definite loss of promin vapor which did not reach the lungs. The method of administration, therefore, involved some inherent difficulties. Close supervision was necessary, since patients taking the drug over a long period of time were apt to get careless.

Moreover, promin is absorbed in the saliva and then expectorated. This was determined in 7 cases and the absorption varied from 70 to 300 mg. of promin per 100 cc. saliva. Although approximate, these figures show that saliva absorption is a factor to be considered in estimating the amount of promin that reaches the lungs.

The most common effect of promin administration was cyanosis. This was present in 23 of the 24 cases. It usually appeared in the early part of the first week and only occasionally during the second week. Invariably it was of slight degree and of short duration. In no instance was the therapy interrupted because of the cyanosis.

In 4 instances promin caused gastric symptoms or headache, or a combination of the two. The symptoms appeared after a month or two of therapy, were slight, temporary and did not require alteration in the treatment.

In 2 cases (nos. 3 and 4, table 1) the treatment was stopped because of toxicity, evidenced by an increase in the icteric index. One patient had promin for eight weeks and the other for fourteen weeks. The icteric index rose to 21 and 22, respectively, and was associated in one case with abdominal pain, and in the other with headache, nausea, vomiting and jaundice. Within two weeks after the discontinuation of the promin, the icteric index became normal and the symptoms disappeared.

In half of the cases there was a mild anaemia. This decrease in haemoglobin occurred usually at the end of the third or fourth week of therapy. The fall in haemoglobin varied between 2 and 4 g. per 100 cc. of blood. However, the anaemia was temporary and usually the haemoglobin returned to normal within two weeks, without modifying the amount of promin and without the use of liver and iron preparations.

There were no cases of leukopenia and, though the white blood cell count showed some variations, none were considered of an abnormal degree and in no case was there any persistent decrease in the white cell count.

The sedimentation rate showed little change. In 4 patients there was a decrease of 7 to 10 mm. in the sedimentation rate after several weeks of therapy associated with an improved chest lesion. In one case there was an increase of 10 to 15 mm. in the sedimentation rate which was related to a progressive pulmonary lesion.

The sputum findings are shown in table 2.

These figures reveal that only 7, or 29 per cent of the group, showed beneficial changes, and even in this improved group only 4, or 16.6 per cent, had permanent sputum conversion.

TABLE 2

*Sputum findings**

UNIMPROVED			IMPROVED		
Before promin	With promin	Number	Before promin	With promin	Number
Usually or always positive	Usually or always positive	11	All positive	All negative	2
			Usually positive	All negative	1
Occasionally positive	Occasionally positive	1	Positive gastric	All negative	1
			Usually positive	All negative except 1 positive gastric	2
Positive gastric cultures only	Positive gastric culture	1			
One positive culture	Frequent negative sputa, then positive	1	Usually positive	All negative except 1 positive sputum	1
Always positive	Frequent negative sputa, then positive	1	UNCHANGED		
			All negative	All negative	1
All negative	All negative except 1 positive gastric culture	1			

* "All negative" means all sputa, gastrics and cultures were negative.

A bacteriological study was made of the sputum of the 21 patients at Otisville before the promin therapy was started, in order to determine the non-acid-fast organisms. These organisms were graded as follows:

4. Many organisms
3. Moderate number of organisms
2. Few to moderate number of organisms
1. Few organisms

These organisms were rechecked after one month and two months of promin therapy. A reduction occurred in 13, or 62 per cent, of the cases. The changes are shown in table 3.

Since the majority of patients had treatment for more than three months, these findings would be more conclusive if the final check-ups of the non-acid-fast organisms had been done.

As indicated in table 3 there was no direct relationship between the changes produced in the non-acid-fast organisms and the concentration of the promin.

In no case did the urinary findings warrant a modification of the dosage. However, 15 patients (7 male and 8 female) showed some urinary changes. Albumin was found 40 times (one-plus on 39 occasions and three-plus on one), and usually appeared between the third and eighth weeks. The 8 female pa-

tients showed only a few white blood cells and no casts; the male patients had a few white blood cells and an occasional granular or hyaline cast. All of these conditions cleared spontaneously.

Of the 24 cases, 2 showed no change in weight, 16 lost weight and 6 gained.

The patients had chest X-ray films every three weeks during the promin therapy. The roentgen studies of each group will be described.

TABLE 3

Changes in non-acid-fast organisms

	AVERAGE BLOOD LEVEL OF PROMIN IN CASES (MG. PER 100 CC. OF BLOOD)
From grade 4 to 1	
2 cases	1.05
From grade 3 to 1	
3 cases	.88
From grade 4 to 2	
1 case	1
From grade 4 to 3	
3 cases	1.45
From grade 2 to 1	
1 case	1.29
From grade 3 to 2	
3 cases	1.26

Group 1—Cavitary lesions: These were subdivided into two types: (*a*) recent and (*b*) old.

(*a*) Three patients (nos. 5, 20, 21, table 1) had recent cavities. In each case there was a single, small, moderately thick-walled cavity with very little surrounding infiltration. All these cases were failures and no significant or permanent changes occurred.

(*b*) This series consisted of 5 cases (nos. 9, 16, 22, 23, 24, table 1). Four had far advanced upper lobe cavitation, and one, a moderately advanced cavernous lesion. The results were unsatisfactory in all cases and all had progressive changes of some sort during the therapy. Three patients showed an increase in the cavitary lesions, and in the 2 with unchanged cavitations a soft, mottled, parenchymal spread appeared in one and a pleural effusion in the other.

Group 2—Soft or fresh lesions: This group consisted of 6 patients (nos. 1, 10, 11, 12, 15, 17, table 1) who, while under sanatorium observation, presented new, soft, fresh areas of infiltration on radiographic examination. Five cases were moderately advanced in extent and one was minimal.

Only one of these patients showed X-ray evidence of clearance of the lesion (slight to moderate resolution in three weeks and then more fibrosis after a period of three and a half months) and sputum conversion. Even in this case the resolution was not unusually rapid. Two other patients showed clearance of the fresh spread, slight in one and marked in the other, but in each a new minimal area of soft infiltration appeared during the period of promin therapy and then resolved during a three-week period. In neither of these cases did sputum conversion occur. In one case the lesion was unchanged for two months; there was slight resolution at the end of the third month, but without sputum conversion. The treatment was a complete failure in 2 cases, with the lesion unchanged in one and worse in the other. The sputum findings were also unchanged.

Group 3—Exudative-productive lesions: In this group there were 5 patients (nos. 2, 4, 6, 8, 19, table 1) with mixed infiltrations or exudative-productive lesions. In 2 the exudative element predominated, in one the productive.

Of this group, one case progressed slightly, one was unchanged, 2 showed trifling improvement and one had definite slight resolution. The X-ray evidence of improvement was not so rapid or marked that it could not have occurred with bed-rest alone. However, 4 of the patients had improved sputum findings as soon as the promin was started. Two of these were completely converted, one had only a single gastric specimen which was negative on culture, and another had only one positive sputum. Three of these patients continued well after the promin was stopped; they became ambulatory and according to X-ray examination their lesions remained stable.

Group 4—Endobronchial ulceration: There were 3 cases (nos. 3, 18, 13, table 1).

Case 1 (no. 3, table 1). In spite of a bilateral fibrocalcific lesion, the sputum was usually positive. Bronchoscopy, on January 30, 1943, revealed in the left lower lobe an ulcer, measuring 8 by 12 mm. After the false membrane was wiped from its surface, a deep, pitted, bleeding depression remained, which was cauterized with 50 per cent silver nitrate. Bronchoscopy, repeated on April 24, 1943, showed that the ulcer was replaced by a small area of bluish granulation which bled easily on being touched and was not considered healed. On April 28 promin was started and continued for eight weeks. Another bronchoscopy, on July 10, 1943, showed the previously ulcerated area to be covered with a healthy, firm granulation tissue infiltrated with scar tissue which did not bleed easily on being touched. Simultaneously with the ulcer healing, the usually positive sputa became negative except for one specimen.

Case 2 (no. 18, table 1). This patient had a technically satisfactory right pneumothorax but gastrics were persistently positive. Bronchoscopy, on March 29, 1943, revealed a deep ulcer covered by a false membrane in the right stem bronchus beginning opposite the upper lobe branch and extending downward as far as could be seen. It had already eroded the cartilage rings which appeared as pointed elevations. The lumen was collapsed and filled by a false membrane so that it was completely closed. Drainage from the lung was badly impaired. It was the bronchoscopist's opinion that putrefaction had already begun and it was feared the lesion would lead to stenosis above the contracted suppurative lung. To counteract the putrefaction and ulceration, promin was

started on June 8, 1943. Bronchoscopy on June 12 showed that drainage had decreased, the false membrane was thinner, the lumen of the bronchus was partially opened, and the evidence of putrefaction had disappeared. The pneumothorax was relaxed immediately after the first bronchoscopy in May, which might account for some of the bronchoscopic changes; still the rapid improvement was believed to be due in some measure to the promin which was continued until August 25, 1943. In the meantime, absorption of the pneumothorax had occurred, so that by August 30 the right lung was expanded 50 to 60 per cent. Another bronchoscopic examination, on September 18, 1943, showed the mucous membrane in the right stem bronchus was smooth and velvety, and drainage from this lung appeared satisfactory.

Case 3 (no. 13, table 1). This was a case of bilateral pneumothorax with endobronchial changes. Promin was given for two and a half months. The pulmonary and bronchial condition remained unimproved.

The rapid improvement in the bronchial picture in 2 of the cases with coincident conversion of the sputum would suggest that promin exerted a beneficial influence. However, its value is somewhat uncertain because of the presence of pneumothorax in one case, where relaxation of the collapse alone might influence the healing of the bronchial ulceration, and the preceding use of silver nitrate and beginning healing in the other patient.

Group 5—Bronchiectasis: This series consisted of 2 cases with bronchiectasis, associated with old tuberculosis.

Case 1 (no. 7, table 1). This patient had a fibrocavernous involvement of both upper lobes, more of the right. There was daily expectoration of a half cupful of thick yellowish-green sputum, often malodorous, with occasional periods of streaking. Sputum was negative for many years, but recently it had occasionally been positive. Many rhonchi and large moist râles were heard over both upper lobes, especially the right. Promin was started on April 28, 1943 and continued for three months. Usually only traces appeared in the blood and there was a question whether the patient was taking the drug properly. Within two months, however, the sputum became more liquid and less purulent, although the amount was unchanged. It remained clear, though positive for tubercle bacilli. The non-acid-fast organisms, which were graded as group 3 at the beginning, changed to a group 1 rating in one month and group 2 after two months. No changes were revealed by X-ray or physical examination. This case was considered slightly improved.

Case 2 (no. 14, table 1). This patient expectorated daily half a cupful of thick greenish sputum which often had an unpleasant odor. Physical examination revealed wheezing in the entire chest, more on the right, and many moist râles in the upper lobes, especially the right. The fingers were slightly clubbed. X-ray films showed a productive lesion in the right upper lobe down to the second anterior rib, with many small areas of rarefaction. A slight similar involvement of the left upper lobe from the apex to the second interspace was found. The trachea and mediastinum were retracted to the right. Lipiodol installation showed marked diffuse saccular bronchiectasis of the right upper lobe, similar changes, less extensive, in the left upper lobe, and a few dilatations in the left base. Bronchoscopy on April 24, 1943 showed in both upper lobe branches a marked infiltrative reaction with oedema and cyanosis, and the left branch was stenotic. Promin

was given from April 28 to July 17, 1943, with fairly good blood levels. After two and a half weeks' treatment the expectoration had increased to two cupfuls a day, but within the next month it decreased to one cupful daily. The sputum had changed to clear white and lost its disagreeable odor. Wheezing occurred seldom and the patient breathed with ease. Physical examination revealed a marked decrease in the wheezing and râles, with the chest usually entirely clear, though later an occasional crepitant râle was heard. The non-acid-fast organisms decreased from group 3 to group 1 in one month and remained so until the treatment was stopped. The sputum remained negative and there was only one positive gastric culture. The X-ray picture remained unchanged. A follow-up report ten months after discharge revealed the cough and expectoration had practically disappeared, the patient had gained weight and was working.

These 2 cases suggest that promin may have beneficial effects in secondary lung suppuration. The improvement in the first case was slight, possibly because of poor administration of the drug and its slight absorption. The second case showed a remarkable result; the sputum lost its purulent and malodorous character, together with improvement in the physical and bacteriological findings.

The changes in the cough and expectoration for the entire series of patients present interesting data. The cough was unaltered in 8 patients, definitely less in 3, and in 2 patients, after various periods of improvement, a slight cough remained; but in 11 cases (46 per cent) the cough was increased. The question arises whether promin may irritate the bronchi, causing an aggravation of the cough. Of these 11 cases, 6 had a parenchymal spread and it might be argued that the increased cough resulted from the progression of the parenchymal process and was not the cause of the dissemination. Yet in 5 instances the cough became worse without a change in the lung lesions, indicating the possible irritative effect of the promin.

The modifications in expectoration are of importance in relation to this question. The expectoration remained unaltered in 9 cases, decreased in one, was the same in quantity though altered in character (from a thick purulent type to a thin, less purulent character) in 3, and increased in 11 cases. The easier expectoration was associated with very thick sputum in 4 cases, while in the other 7 the sputum was thin. Three of these 11 patients showed that the bronchial irritation and enhanced cough and expectoration might be directly responsible for the progression of the lesion. The exaggerated cough and expectoration preceded the roentgenological appearance of the spread by one and a half, two, and three weeks, respectively. The increase of cough and expectoration in many of these cases is, therefore, a possible source of danger; the more frequent cough with a more copious expectoration may disseminate the infection. The thinning and clearing of the sputum would, however, be an advantage in nontuberculous lung suppurations.

COMMENT

Inasmuch as this is a small series of cases, no final conclusions as to the use of vaporized promin can be made, but our experience would justify a preliminary evaluation of this form of therapy.

Of the three groups of tuberculous lesions treated, the mixed or exudative-productive type of infiltration with positive sputa—the type of case ordinarily requiring an extended period of bed-rest—showed the most favorable results.

It is impossible to make any decisions about therapy used in only 3 cases, especially when these were not ideally chosen. Yet the favorable changes in endobronchial ulceration in 2 of the 3 cases are encouraging. Endobronchial ulceration is one of the most difficult complications of tuberculosis to treat successfully and any therapeutic measure that can be applied without danger should receive an adequate trial. Further experimentation with promin in this condition seems to be indicated.

Promin was used in only 2 cases of bronchiectasis and therefore no conclusions are warranted, but the mild improvement in one and the marked beneficial change in the other indicate a possible therapeutic effect. Improvement in bronchiectasis with the use of nebulized sodium sulfathiazole (18) and intratracheal and intrabronchial instillations of a 5 per cent aqueous suspension of microcrystalline sulfathiazole (19) has been reported. Further use of promin in lung suppuration of a nontuberculous nature should be considered. It may be that this will be its field of greatest usefulness.

The result in endobronchial ulceration raises the question of the direct topical effect of the promin. It has been shown (19) that, after the intratracheal or intrabronchial instillation of microcrystalline sulfathiazole suspension, significant concentrations persisted for twenty-four to forty-eight hours. We have not determined promin levels in bronchial secretions. However, the improvement in endobronchial ulceration and bronchiectasis would indicate the presence of promin in bronchial secretions and a topical effect of promin.

As shown by the results above, the direct topical effect of promin in pulmonary tuberculosis has not been very satisfactory or significant. The administration of the drug by vaporization was not a simple or entirely satisfactory method. The treatments had to be constantly supervised. The coöperative ability of the patients varied while the procedure had to be continued over a long period of time. Variations in absorption of the promin were great and no constant blood level could be obtained. The absorption of the drug in the saliva was also a source of loss. This could perhaps be remedied by the use of an L-shaped stem on the atomizer, similar to the shape of the quartz lamp laryngeal applicator used in heliotherapy.

The administration of the drug as practiced in this series is a hospital procedure. Close laboratory supervision of the patients is necessary. Temporary mild anaemias occur which might have been avoided by preliminary iron medication as suggested by Heaf (5). The abnormal urinary findings did not persist. Cyanosis was mild and did not constitute a problem. Toxaemia (increase in icteric index) is an indication for discontinuation of the drug.

Any direct intrabronchial medication in tuberculous patients is not without danger. The increase in cough and expectoration and the liquefaction of the sputum may cause spread of the tuberculous lung lesions, though thinning and clearing of the sputum is beneficial in putrid or purulent pulmonary secretions not caused by tubercle bacilli.

CONCLUSIONS

1. Twenty-four patients with pulmonary tuberculosis received promin by inhalation. The results must be viewed in the light of the difficulties of administration and lack of a high constant concentration of promin in the blood.

2. The promin appeared to be of little value in parenchymal pulmonary tuberculous lesions, possibly because of the inadequate concentration of the drug.

3. Promin inhalation was apparently of some benefit in endobronchial ulceration and demonstrated its best results in one case of bronchiectasis.

4. This study has again demonstrated the possibility of introducing drugs by means of inhalation.

CONCLUSIONES

1. Veinticuatro tuberculosos pulmonares recibieron la promina por inhalación y hay que considerar el resultado a la luz de las dificultades encontradas en la administración y de la falta de una concentración alta constante de la droga en la sangre.

2. La promina pareció poseer poco valor en las lesiones tuberculosas del parénquima pulmonar, posiblemente debido a una concentración inadecuada.

3. La inhalación de promina fué aparentemente de algún beneficio en las ulceraciones endobronquiales y reveló su efecto mejor en un caso de bronquiectasia.

4. Este estudio demuestra de nuevo la posibilidad de introducir drogas por medio de la inhalación.

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STATISTICAL DATA

Edited by MARY DEMPSEY

WHAT IS HAPPENING TO THE TUBERCULOSIS DEATH RATE?

In recent months persons interested in the problem of tuberculosis control, and in fact the general public, have evinced considerable concern regarding the trend of the country's death rate from tuberculosis. Inasmuch as war conditions usually lead to an increase in the incidence of tuberculosis a rise in the death rate was to be expected in 1943, the second full year of the war; for this reason the decline registered is even more encouraging than those recorded in previous years. In view of the chronic nature of the disease, however, several years may elapse before the impact of war conditions is reflected in a mortality rise. In short, we must all realize that the probability of an increase in the incidence of tuberculosis is enhanced each day the war continues.

Provisional reports from the health departments of 48 states and the District of Columbia indicate that the 1943 tuberculosis rate for continental United States was 41.9 per 100,000 population, somewhat lower than the rate of 43.1 in 1942. This decline coincides with the mortality trend in 1943 among policyholders of the Metropolitan Life Insurance Company and also with the trend shown in a preliminary report of the United States Public Health Service; the latter included deaths for the first nine months of 1943 in 37 states and the District of Columbia.

When the United States Bureau of the Census publishes its 1943 *Vital Statistics* report some months hence, the final 1943 death rate for the country as a whole may differ somewhat from the provisional figure given in table 1, but experience over a period of years indicates that the difference will be slight. For the individual states, of course, the variation in death rates may be greater because of the difference in method described in the next paragraph.

Source of data: The number of deaths from tuberculosis and the number of new cases reported for 1943 have been obtained by correspondence with state departments of health. Mortality figures for earlier years have been taken from *Vital Statistics* volumes published by the United States Bureau of the Census.

Unless otherwise stated, the deaths mentioned in this article are those which *occurred* in each state and not the number of deaths among *residents* of each state. While the latter method is greatly to be preferred and is now the only method used by the Census Bureau, it is not possible at this time to obtain figures showing deaths from tuberculosis among the residents of each state in 1943. For this reason all deaths for the years shown are those tabulated by place of occurrence.[1]

Death rates have been computed on the basis of population estimates for July 1, 1940, 1941, and 1942, recently released by the United States Bureau of the

[1] Maryland and the District of Columbia constitute the only exceptions to this procedure. Deaths of District residents which occurred at the District's public sanatorium in Glenn Dale, Maryland, were added to the deaths which occurred in the District and subtracted from the deaths which occurred in Maryland.

TABLE 1

New cases reported, deaths and death rates from tuberculosis, by state, 1943

(Provisional figures as reported by state departments of health)

STATE	NEW CASES REPORTED[1]	NUMBER OF DEATHS (RECORDED)	CASES PER DEATH	DEATH RATE PER 100,000 POPULATION[2]
United States	118,042	56,178	2.10	41.9
Alabama	2,894	1,266	2.29	43.7
Arizona	1,427	884	1.61	125.9
Arkansas	901	933	0.97	49.9
California	7,879	3,809	2.07	45.0
Colorado	1,618[3]	597[3]	2.71	51.3
Connecticut	1,280	599	2.14	33.7
Delaware	137	104	1.32	37.0
District of Columbia	2,410	598[4]	4.03	67.2
Florida	1,211	834	1.45	35.2
Georgia	2,409	1,285	1.87	39.8
Idaho	57	84	0.68	16.9
Illinois	8,756	3,240	2.70	42.1
Indiana	2,749	1,216	2.26	35.8
Iowa	729	380	1.92	16.4
Kansas	669	363	1.84	20.4
Kentucky	2,356	1,748	1.35	64.0
Louisiana	2,090	1,299	1.61	50.8
Maine	588	261	2.25	31.9
Maryland	3,522	1,204[4]	2.93	57.6
Massachusetts	2,960	1,802	1.64	42.3
Michigan	6,546	1,802	3.63	33.2
Minnesota	1,928	753	2.56	29.2
Mississippi	1,637	786	2.08	35.2
Missouri	2,211	1,646	1.34	43.9
Montana	386	199	1.94	41.1
Nebraska	177	199	0.89	16.2
Nevada	75	70	1.07	48.8
New Hampshire	281	128	2.20	27.8
New Jersey	4,051	1,913	2.12	45.2
New Mexico	1,013	389	2.60	72.8
New York	14,744	6,417	2.30	49.9
North Carolina	1,583	1,444	1.10	39.7
North Dakota	317	125	2.54	23.0
Ohio	5,451	2,780	1.96	40.4
Oklahoma	1,751	906	1.93	41.8
Oregon	593	271	2.19	21.9
Pennsylvania	5,404	3,746	1.44	39.6
Rhode Island	861	283	3.04	37.7
South Carolina	635	645	0.98	33.1
South Dakota	265	154	1.72	26.7
Tennessee	3,793	1,883	2.01	63.6
Texas	7,311	3,278	2.23	47.0
Utah	194	65	2.98	10.3
Vermont	137	117	1.17	35.7
Virginia	3,771[5]	1,397	2.97[5]	45.4
Washington	1,717	717	2.39	35.3
West Virginia	1,643	765[6]	2.15	43.6
Wisconsin	2,845	750	3.79	24.9
Wyoming	80	44	1.82	17.3
Hawaii	1,087[7]	253	4.30	57.2[8]
Puerto Rico	7,158	4,572	1.57	231.1

[1] Special effort is made to obtain the number of new cases reported exclusive of "primary" or "childhood type" cases which in some states are reportable.

[2] Death rates are based on the population for July 1, 1943, including members of the armed forces in continental United States, but excluding those overseas, as estimated by the U. S. Bureau of the Census.

[3] Figures shown include 1,199 new reported cases and 180 deaths among non-residents.

[4] Deaths of District of Columbia residents which occurred at Glenn Dale Sanatorium in Maryland have been added to the deaths which occurred in the District of Columbia and subtracted from the number which occurred in Maryland.

[5] Cases shown are for pulmonary tuberculosis only. Cases per death are based on 1,270 deaths from pulmonary tuberculosis.

[6] 1942 figure; 1943 data not available.

[7] Includes reactivated cases as well as new cases.

[8] Based on the population in 1942, as estimated by the U. S. Bureau of the Census.

Census in Special Reports on Population, Series P-44, No. 11. Population estimates for July 1, 1943 have been taken from a similar release, Series P-44, No. 16.

These population estimates for recent years include members of the armed forces who were stationed in each state on the estimate date. They do not include military and naval personnel who may be residents of the state but who were stationed overseas on the date in question.

Factors in the continued decline in tuberculosis mortality: The decline in tuberculosis mortality has continued steadily each year since 1936 and, with the exception of two minor interruptions, each year since 1918. These sustained decreases must be attributed to quite a number of factors, some of which are intangible.

1. Greatly improved and enlarged facilities for the care of the tuberculous, including better managed sanatoria and thousands of additional beds; a higher standard of clinic service and of public health nursing service, as well as a great improvement in health administration generally.

2. Earlier diagnosis and improved methods of diagnosis, including mass X-ray surveys among apparently healthy adults.

3. Recognition on the part of patients and their families of the importance of sanatorium care with the result that a much larger proportion of infectious patients have been segregated, thus minimizing the spread of the disease.

4. Increasing awareness of the tuberculosis problem and acceptance of the greatly amplified program of health education.

5. Decided improvement in the standard of living throughout the country.

6. Intensive efforts directed toward certain groups, such as high school and college students, medical students, nurses, expectant mothers and young women generally; more recently these efforts have been directed toward industrial employees, Negroes and Spanish-speaking people, and men and women who are being examined for service in the armed forces.

States with recently increased mortality: In spite of the fact that in 1943 the provisional death rate from tuberculosis was 2.8 per cent lower than the final death rate published by the Census Bureau for 1942, in 21 states the 1943 mortality from the disease represented an increase when compared with the 1942

figures. The *actual number* of deaths increased in 18 of the 21 states, while declines in population account for the increased *death rates* in the remaining 3 states.

Table 2 enumerates those states in which the provisional death rates from tuberculosis increased between 1942 and 1943.

TABLE 2

States in which the death rates[1] from tuberculosis increased between 1942 and 1943

STATE	DEATHS FROM TUBERCULOSIS		DEATH RATES FROM TUBERCULOSIS PER 100,000 POPULATION	
	1943	1942	1943	1942
Arkansas	933	963	49.9	48.6
Colorado	597	567	51.3	51.1
Georgia	1,285	1,274	39.8	39.6
Illinois	3,240	3,273	42.1	40.8
Kentucky	1,748	1,734	64.0	62.2
Louisiana	1,299	1,274	50.8	50.0
Maine	261	247	31.9	29.8
Massachusetts	1,802	1,616	42.3	37.2
Minnesota	753	710	29.2	26.6
Missouri	1,646	1,507	43.9	39.7
Montana	199	196	41.1	38.1
Nebraska	199	179	16.2	14.4
New Hampshire	128	112	27.8	23.2
New Jersey	1,913	1,868	45.2	43.6
New Mexico	389	319	72.8	60.3
New York	6,417	6,188	49.9	47.7
North Dakota	125	118	23.0	20.2
Rhode Island	283	269	37.7	36.3
Vermont	117	107	35.7	31.3
Wisconsin	750	762	24.9	24.4
Wyoming	44	36	17.3	14.3

[1] These figures which were reported by the state departments of health are based on tuberculosis deaths which *occurred* in each state and not on deaths among *residents*; 1943 figures are provisional. The figures reported by the state health departments for 1942 have been adjusted very slightly so that the total number of deaths from tuberculosis in the United States would agree with the final figure reported by the Census Bureau.

The fact that in 1943 the death rate increased in 21 states is not of itself significant. Each year, according to table 3, a certain number of states record higher rates than in the year immediately preceding, even though a definite decline in tuberculosis mortality has occurred in the country as a whole. Surprisingly enough, the number of states with advancing death rates has steadily increased each year for the past six years.

TABLE 3

The number of states with increased death rates from tuberculosis and the percentage of decline in the tuberculosis death rate for continental United States, classified by the years compared: 1937–1943

YEARS COMPARED	NUMBER OF STATES WITH INCREASED DEATH RATES FROM TUBERCULOSIS	PERCENTAGE OF DECLINE IN THE DEATH RATE FROM TUBERCULOSIS IN CONTINENTAL UNITED STATES
1943, compared with 1942	21	2.8
1942, compared with 1941	17	3.1
1941, compared with 1940	11	2.8
1940, compared with 1939	9	2.8
1939, compared with 1938	8	4.1
1938, compared with 1937	6	8.7

Variation in trend of mortality in different sections of the country: The most interesting trend noted in 1943 is the fact that so many of these increased death rates are concentrated in the industrial states of the northeastern and north central sections of the country, while even more pronounced declines are noted in the states of the South and West.

Can these changes be attributed to the internal migration of the past few years which has altered not only the size but also the composition of the population in certain regions? Unfortunately at present this question cannot be answered.

Table 4 indicates the extent to which the current trend of tuberculosis mortality varies in the different geographical divisions of the country.

TABLE 4

Death rates[1] from tuberculosis per 100,000 population and percentage of increase or decrease in death rates, classified by region and geographical division: 1940–1943

REGION AND GEOGRAPHICAL DIVISION	DEATH RATES FROM TUBERCULOSIS PER 100,000 POPULATION				PERCENTAGE OF INCREASE OR DECREASE IN DEATH RATES		
	1943	1942	1941	1940	1942–1943	1941–1942	1940–1941
United States	41.9	43.1	44.5	45.8	−2.8	−3.1	−2.8
The Northeastern States	43.7	42.7	42.2	42.3	+2.3	+1.2	−0.2
New England	38.0	34.7	35.7	35.1	+9.5	−2.8	+1.7
Middle Atlantic	45.5	45.2	44.3	44.5	+0.7	+2.0	−0.4
The North Central States	34.2	33.7	34.9	35.6	+1.5	−3.4	−2.0
East North Central	37.1	36.9	38.2	39.0	+0.5	−3.4	−2.1
West North Central	28.3	27.1	28.3	28.7	+4.4	−4.2	−1.4

[1] These death rates are based on tuberculosis deaths which *occurred* in each state and not on deaths among *residents*; 1943 death rates are provisional.

TABLE 4—*Continued*

REGION AND GEOGRAPHICAL DIVISION	DEATH RATES FROM TUBERCULOSIS PER 100,000 POPULATION				PERCENTAGE OF INCREASE OR DECREASE IN DEATH RATES		
	1943	1942	1941	1940	1942–1943	1941–1942	1940–1941
The South	46.7	50.7	54.1	56.5	−7.9	−6.3	−4.2
South Atlantic	42.9	47.0	50.5	53.6	−8.7	−6.9	−5.8
East South Central	52.5	57.7	62.0	62.3	−9.0	−6.9	−0.5
West South Central	47.3	50.3	52.6	55.8	−6.0	−4.4	−5.7
The West	44.1	47.5	48.8	52.1	−7.2	−2.7	−6.3
Mountain	52.8	52.9	53.9	57.3	−0.2	−1.9	−5.9
Pacific	40.9	45.4	46.7	49.9	−9.9	−2.8	−6.4

Although many of the changes in death rates enumerated in table 4 are too trivial to warrant serious consideration, the fact emerges that tuberculosis mortality has shown a rather definite tendency to rise in the northeastern states with a slight recent increase in the north central states. On the other hand, declines noted in the death rates of the states in the South and West have been pronounced and consistent during the past three years.

States in which tuberculosis mortality has definitely declined: The tuberculosis death rates in 26 states declined to some extent in 1943, as compared with 1942, while in 10 of these states the decreases registered were more than 5 per 100,000 population. Southern states are conspicuous in the group with pronounced declines, as shown in table 5.

TABLE 5

States in which tuberculosis death rates[1] decreased more than 5 per 100,000 population between 1942 and 1943 and percentage of decline in the death rates

STATE	DEATHS FROM TUBERCULOSIS		DEATH RATES FROM TUBERCULOSIS PER 100,000 POPULATION		PERCENTAGE OF DECLINE IN THE TUBERCULOSIS DEATH RATE: 1942–1943
	1943	1942	1943	1942	
Arizona	884	849	125.9	154.3	18.4
California	3,809	3,868	45.0	50.3	10.5
Delaware	104	138	37.0	49.5	25.3
Florida	834	865	35.2	40.4	12.9
Mississippi	786	1,099	35.2	49.3	28.6
Nevada	70	76	48.8	55.9	12.7
Oregon	271	297	21.9	27.1	19.2
Tennessee	1,883	2,114	63.6	71.9	11.5
Texas	3,278	3,591	47.0	53.6	12.3
Virginia	1,397	1,603	45.4	53.0	14.3

[1] These death rates are based on tuberculosis deaths which *occurred* in each state and not on deaths among *residents*; 1943 death rates are provisional.

The effect of marked changes in population distribution is exemplified by the decline noted in the death rate for Arizona where the number of deaths from tuberculosis was actually greater in 1943 than in 1942. This seeming contradiction is explained by the fact that the population of Arizona advanced 27.7 per cent from July 1, 1942 to July 1, 1943, according to estimates published by the Census Bureau.

Deaths from tuberculosis declined most in the State of Mississippi where the number dropped from 1,099 in 1942 to 786 in 1943. The population in this state has remained practically the same *size* in these two years; in fact, it increased but 2.2 per cent between April 1, 1940, the date of the last census, and July 1, 1943.

One wonders to what extent the *composition* of Mississippi's population may have changed since the beginning of the war. We know that large Army and Navy bases are situated in this state and we also know that members of the armed forces stationed in the state are included in the population estimates.

Fairly well authenticated rumors indicate that vast numbers of Negroes have left Mississippi in the last few years in an effort to seek employment in the North and Far West. If, for example, 50,000 or 100,000 Negroes of both sexes, all ages, and in all stages of health had left the state in the past year or two, and if, in the same period, an equal number of young soldiers and sailors who had recently been examined and found to be sound were assigned to this state, it is conceivable that the number of tuberculosis deaths might decline to a remarkable degree, even though the size of the population was unchanged. Unfortunately no data are available to prove or disprove this interesting theory.

Population estimates: According to the Census Bureau release, the population estimates used in this article "are based partly on war ration book registration data and partly on statistics of births and deaths, by states, since the 1940 Census. Allowance is made for net immigration into the United States and for armed force strength, by states. Members of the armed forces stationed outside continental United States are excluded entirely."

The abnormal conditions incident to the war have affected the population distribution in the states more than is usually realized. Internal migration, both civilian and military, has resulted in decreased population in the northeastern and north central states, while in the South and West the population has increased materially since the date of the last decennial census in 1940.

Moreover, the mere fact that 2,500,000 of the country's healthiest young men had been sent abroad and for that reason are excluded from the population estimates for July, 1943 tends to raise the death rate for the country as a whole rather than to lower it. Since all (or approximately all) these young men had been recently X-rayed it is highly probable that the deaths from tuberculosis among their number would be negligible in 1943; yet 2,500,000 of them are eliminated from the population base on which the death rate is computed.

The difficulties of computing sound death rates in these days of major population shifts cannot be appreciated until one makes an effort to obtain population estimates for a given date, to evaluate the extent of the changes in a given community, and to analyze the effect of the population changes on the death rates.

For example, the population of the entire country on July 1, 1943 was esti-

mated to be 133,942,410; this figure includes members of the armed forces stationed in this country but excludes those stationed outside continental United States on that date. By comparing this population estimate with the 56,178 deaths from tuberculosis in 1943 we get a death rate of 41.9 per 100,000 population.

On the other hand, the *country's total population including members of the armed forces stationed overseas* was 136,485,262 on July 1, 1943, according to the Census Bureau. Everyone must admit that only an infinitesimal number of deaths from tuberculosis was to have been expected in 1943 among the 2,542,852 members of the armed forces stationed outside continental United States since all had been X-rayed prior to their induction.

Therefore, if the total population figure of 136,485,262 had been related to the 56,178 deaths from tuberculosis, the death rate would have been 41.2 instead of 41.9. In other words, the exclusion of 2,500,000 of the healthiest young men from the population estimate for the country has a definite tendency to lead to an increased death rate in the United States and in each state from all causes or from any specific cause. This tendency will become far more apparent when the 1944 death rate is computed since at least 5,500,000 of the persons least liable to die of tuberculosis are stationed outside the country. If the same number of persons were to die in 1944 as in 1943, the exclusion of 5,500,000 from the population base would result in a death rate of 42.9 instead of 41.9.

Reasons for dependence upon death rates as the best available index of the extent of the disease: There are two major reasons for our continued dependence upon death rates as the soundest measure of the extent of tuberculosis in a given community:

1. In order to evaluate health conditions in two or more communities of different size, we must compare the number of deaths in relation to the population and not just the actual number of deaths which occur in each area studied.

2. Unfortunately the number of cases of tuberculosis which exist in any community at any given time is unknown. Therefore, we do not know the incidence of the disease in any area or in any particular group, though the incidence may be estimated. The actual number of cases remains unknown because—
   a. Many cases, some of which are advanced, have never been diagnosed and even the persons in question do not realize that they are suffering from tuberculosis.
   b. Because of laxity or oversight on the part of the attending physicians not all cases which are diagnosed are officially reported to local health departments in compliance with the law.
   c. Certain small insurance companies still specify that benefits cannot be paid if the decedent died of tuberculosis; under these circumstances the attending physician may be extremely reluctant to report a case of tuberculosis.

New reported cases: In the country as a whole, 118,042 new cases of tuberculosis were reported to state health departments during 1943. Since 56,178 persons died of the disease during the year, according to provisional figures, the ratio of new reported cases to deaths was 2.10.

This ratio of new cases reported in one year per death in that year has advanced from 1.48 in 1930 to 2.10 in 1943, but not each year has seen an increase. No doubt the examinations of men about to enter the armed forces, together with the mass X-ray surveys in industry, have accelerated the improvement in case reporting noted since 1941. (See table 6.)

Not until 1942 did the ratio of new reported cases per annual death attain the minimum goal of 2 in the United States as a whole. For many years the appraisal form of the American Public Health Association's Committee on Administrative Practice indicated that 2 new cases should be reported each year per death from tuberculosis in that year; recently, however, this standard has been raised to 3 new reported cases per annual death.

This current improvement in case reporting is vividly illustrated by the morbidity report of the United States Public Health Service for the first quarter of 1944 when 30,902 new cases of tuberculosis were reported, compared to 27,061 during the first quarter of 1943.

TABLE 6

New cases reported,[1] deaths from tuberculosis,[2] and new cases reported per death, classified by year: death registration states, 1930–1943

YEAR	NEW CASES REPORTED[1]	DEATHS FROM TUBERCULOSIS[2]	NEW CASES REPORTED PER DEATH IN ONE YEAR
1943	118,042	56,178	2.10
1942	117,221	57,690	2.03
1941	106,413	59,251	1.80
1940	100,772	60,428	1.67
1939	101,470	61,609	1.65
1938	107,021	63,735	1.68
1937	112,394	69,324	1.62
1936	107,086	71,527	1.50
1935	111,856	70,080	1.60
1934	113,020	71,609	1.58
1933	114,412	74,842	1.53
1932	120,693[3]	74,267[3]	1.63
1931	123,792[3]	80,129[3]	1.54
1930	123,754[3]	83,352[3]	1.48

[1] Provisional figures reported by state health departments.

[2] 1943 deaths represent provisional figures reported by state health departments; deaths for earlier years are final figures published by the Census Bureau.

[3] Exclusive of Texas which was admitted to the death registration area in 1933; new reported cases in the United States including Texas were 121,691 in 1932, 124,858 in 1931, and 124,940 in 1930.

So far as case reporting is concerned, the District of Columbia made a better record than any of the states, since 4.03 new cases were reported in 1943 per death from tuberculosis in that year. States with excellent records in this respect were Wisconsin, Michigan and Rhode Island, each of which had a ratio of more than 3 new reported cases per annual death. On the face of it, Hawaii's record of 4.30 new cases reported per death in 1943 looks impressive, but the provisional information received from Hawaii states that reactivated cases are included among the case reports. (See table 1.)

Case reporting is very poor indeed in the states of Idaho, Nebraska, Arkansas and South Carolina. In each of these states less than one new case per death was reported in 1943. It is evident that an intensive campaign for more complete reporting of tuberculosis cases is urgently needed in these states.

Figures on case reporting are difficult to analyze because local practice varies so widely. In some states one reported case is added to the roster every time a death certificate is filed on which tuberculosis appears as the cause of death. Certain communities include cases reported after death while others exclude from their reported cases those not known prior to death.

A few states continue to report cases of primary tuberculosis or healed tuberculosis, with the result that a good record for case reporting may be established which is more apparent than real. The possibility of these variations in practice needs to be understood whenever the completeness of case reporting is under discussion.

In May, 1944, the American Trudeau Society at its annual meeting in Chicago adopted a standard definition that determines which cases of tuberculosis are considered reportable. This definition is as follows:

"Cases to be reported should include all cases of reinfection type pulmonary tuberculosis which are classified as active, quiescent, apparently arrested or arrested; cases of *active* primary tuberculosis; cases of acute pleural effusion which are either definitely or presumably tuberculous; and cases of active non-pulmonary tuberculosis."

Case reporting among whites and Negroes: In 1943 an effort was made to obtain from the state health departments in each of the southern states provisional data showing new cases reported, as well as deaths from tuberculosis, separately for whites and Negroes. The lack of recent population estimates for the two groups, by state, has made the computation of death rates for whites and Negroes impossible at this time.

In spite of this inability to determine tuberculosis mortality by color for each state, data submitted by the state health departments made it possible to ascertain for each racial group the ratio of new reported cases per death in 1943. Table 7 which gives these ratios includes all those states in which Negroes comprise 10 per cent or more of the total population.

TABLE 7

New cases reported, deaths from tuberculosis, and ratio of new reported cases per death among whites and Negroes in selected southern states:[1] 1943

STATE	NEW CASES REPORTED		DEATHS FROM TUBERCULOSIS		RATIO OF NEW REPORTED CASES PER DEATH	
	White	Negro	White	Negro	White	Negro
Alabama	1,433	1,461	492	774	2.91	1.89
Arkansas	657	244	525	408	1.25	0.60
Delaware	63	74	51	53	1.24	1.40
District of Columbia	1,447	963	191	407	7.58	2.37
Florida[2]	738	471	363	471	2.03	1.00
Georgia	1,175	1,234	486	799	2.42	1.54
Louisiana	1,165	925	506	793	2.30	1.17
Maryland	2,237	1,285	650	554	3.44	2.32
Mississippi	741	896	232	554	3.19	1.62
North Carolina	795	788	597	847	1.33	0.93
South Carolina	[3]	[3]	161	484	[3]	[3]
Tennessee	2,720	1,073	1,218	665	2.23	1.61
Texas	[3]	[3]	2,626	652	[3]	[3]
Virginia[4]	2,445	1,326	601	669	4.07	1.98

[1] States selected are those in which Negroes comprise 10 per cent or more of the total population.

[2] Excludes 2 cases reported among Chinese.

[3] Data not available.

[4] Virginia figures represent cases and deaths of pulmonary tuberculosis only.

In every state except Delaware where extremely small numbers are involved, the ratio of new reported cases per death is conspicuously higher among white persons than among Negroes. Numerous explanations might be suggested as the reason for this finding; among them is the generally accepted theory that tuberculosis runs a very rapid course in Negroes, so that at any one time fewer cases per death probably exist among their number. Moreover, their lower economic status and fewer opportunities for education may result in a tendency to postpone medical consultation.

Presumably the unusually high ratio of reported cases in the District of Columbia is partially traceable to the mass X-ray surveys conducted during 1943 in the offices of the Federal Government and elsewhere. Then, too, one must realize that the District is a densely populated urban community in which health conditions differ from those in the states.

Students of the tuberculosis problem recognize the fact that data on case reporting usually reflect the general adequacy of health administration in a community; because of the many uncertainties involved, however, they are not indicative of the incidence of tuberculosis in the group or area studied.

SUMMARY

This article brings up many questions with reference to the future trend of tuberculosis mortality. Unfortunately these questions cannot be answered with any degree of certainty at the present time.

Some persons are of the opinion that the increased-death rates from tuberculosis in the industrial states of the northeastern and north central sections of the country may presage rising mortality in the country as a whole. Is it not more probable that the stupendous migration of the past few years has resulted in a realignment of the American people—to some extent, at least, on health grounds? Only time can determine which of these two hypotheses is correct.

The assignment of millions of the country's healthiest young men and young women outside continental United States and the elimination of their number from population estimates have had the effect of raising the tuberculosis death rate slightly in the country as a whole. Many more millions of our healthiest young citizens have been assigned to camps which are largely concentrated in the states of the South and Far West where climatic conditions facilitate military training throughout all months of the year.

Simultaneously other millions of all ages whose state of health is unknown have migrated to and fro without pattern in search of industrial employment. It is quite possible that this population upheaval, which has no parallel in our history, will affect the trend of tuberculosis mortality in the states for some years to come.

Changes in the *size* of a state's population are allowed for when death rates are computed on the basis of the best available population estimates. But changes in the *composition* of the population cannot be taken into consideration until a new population census has been taken; and no population census will prove to be worth while until the country has had a few years to settle down after the war.

In any case, persons interested in the program of tuberculosis control are warned that comparisons of tuberculosis death rates in states, cities and counties cannot be made from year to year on a sound basis, as has been the case in the past.

SUMARIO

Suscítanse aquí muchos puntos relativos a la futura tendencia de la mortalidad tuberculosa, aunque por desgracia no pueden ser resueltos todavía con mayor certeza.

Opinan algunos que el aumento de la mortalidad tuberculosa en los estados industriales del nordeste y norcentro de los Estados Unidos acaso augure un aumento semejante para el país en conjunto. ¿No es más probable que la estupenda migración de los últimos años haya dado por resultado cierto realineamiento del pueblo estadounidense—por lo menos desde el punto de vista sanitario? Sólo el tiempo puede decirnos cuál de estas dos hipótesis está bien fundada.

El traslado al extranjero de millones de los jóvenes más sanos de ambos sexos y su eliminación de los cálculos de la población han hecho elevar ligeramente la mortalidad tuberculosa para el país en conjunto. Muchos millones más de los jóvenes más sanos han sido destacados a campamentos concentrados en gran parte en los estados del Sur y del Lejano Oeste en los que las condiciones climatológicas facilitan el adiestramiento militar en todas las épocas del años.

Simultáneamente, millones de sujetos de todas edades cuyo estado de salud se desconoce han migrado de aquí para allí a su albedrío, en busca de empleo

en las varias industrias, siendo muy posible que este disloque de la población, sin paralelo en la historia, afecte la tendencia de la mortalidad tuberculosa por muchos años después.

Al computar los coeficientes de mortalidad tomando por base los mejores cálculos posibles de la población se toman en cuenta los cambios en el *número* de los habitantes de un estado, pero no pueden considerarse los cambios en la *composición* de la población sino después de hacer un nuevo censo, y ningún censo servirá de mayor cosa hasta que el país haya tenido algunos años para tranquilizarse después de la guerra.

De todos modos, los interesados en la lucha antituberculosa deben tener presente que ya no hay bases sólidas para comparar de año en año, como se hacía en el pasado, la mortalidad tuberculosa de los distintos estados, distritos y ciudades.

Edward S. McSweeny

1877–1944

The fight against tuberculosis lost a valiant soldier in the death of Dr. Edward S. McSweeny on September 17, 1944.

A native of New York City, Doctor McSweeny received his degree in medicine from New York University in 1897. Following postgraduate studies abroad, he

Edward S. McSweeny
1877–1944

became Superintendent of Otisville Sanatorium in 1906 and remained in that position until he became Superintendent of Sea View Hospital in 1912. In 1917 he resigned and became Director of the Medical Department of the New York Telephone Company, which position he retained for twenty-five years until his retirement in 1942.

Doctor McSweeny was, for a number of years, Secretary-Treasurer of the American Sanatorium Association, later becoming its President. He served on the Board of the National Tuberculosis Association in 1936 and has been a member of the Board of Directors of Potts Memorial Hospital, Stony Wold Sanatorium and the Tuberculosis Preventorium for Children in Farmingdale, New Jersey.

In 1933 Doctor McSweeny was appointed Chairman of the Tuberculosis Committee of the New York Tuberculosis and Health Association and served in that capacity for ten years. He served also as a member of the Board of Directors of the Association until his death.

Other positions which Doctor McSweeny held were Chairman of the Medical Board of the New York Teachers Retirement System, Consultant to Grasslands Hospital, Westchester County, and St. John's Hospital, Long Island City.

A list of his activities gives only a vague picture of Doctor McSweeny's actual contribution in the field of tuberculosis control and treatment. His long service as Medical Director of the New York Telephone Company coincides with the rapid development of industrial hygiene and he was among the pioneers in this branch of preventive medicine which has proved so significant a factor in the progressive reduction of tuberculosis mortality.

He will be remembered by his many friends for the incisive quality of his thinking, for his good judgment, and for his devotion and enthusiasm toward the work in hand. Although he assumed willingly many responsibilities, he was neglectful of none and was faithful in attendance at the meetings of committees on which he served and invariably constructive in his advice and suggestions. Although unyielding when he knew himself to be in the right, he was never antagonistic and retained the friendship and deep respect of his associates, even when differing with their opinions.

Those who knew him well, felt for him not only a warm personal affection but sincere regard for his high character and for his unremitting devotion to his professional work.

KENDALL EMERSON

AMERICAN TRUDEAU SOCIETY

Report of the Committee on Undergraduate Medical Education

Dr. Frank L. Jennings, *Chairman*

Dr. R. G. Bloch
Dr. Harold M. Coon
Dr. Reuben J. Erickson
Dr. C. Howard Marcy
Dr. Sidney J. Shipman
Dr. John Skavlem

During the past year the Committee has visited ten medical schools. It is felt that the visiting of the medical schools by the Committee as a whole, or in part, is a much more satisfactory method of reviewing the situation in the schools than would be a visit by one member of the Committee, and that it is far superior to obtaining the information by the questionnaire method.

The Dean of every Medical School has been interviewed, and in many schools several members of the faculty have also been interviewed. In each school, inquiry has been made as to the methods of teaching chest diseases, particularly tuberculosis, the sanatorium affiliation and method of caring for the student health. It has been the policy of the Committee to act as a collector and disseminator of information regarding the teaching of chest diseases rather than as an investigating body.

Several interesting things have been ascertained from our interviews and some of these are listed:

1: In one school a great deal of stress is put upon fluoroscopy of the chest because it is felt that in the not too distant future many more fluoroscopes will be used, and that the student should be thoroughly familiar with their use.

2: In one state, two schools excused their students from routine class work so that they might devote an entire day to a symposium given on tuberculosis.

3: It was found that the clerkship in one school was particularly well organized. In this school each student was given a manual which presented the essential facts on tuberculosis, and gave pertinent information about the Sanatorium where the clerkship was held.

4: In another school students were taught chest diseases in small groups rather than trying to teach the class as a whole.

5: A course called "Living Anatomy" was taught in one school. The Dean in this school feels that it has a very direct relationship to chest diseases and for that reason allows forty hours for this course.

6: In another school two X-ray films are taken annually of each student. The reason this was put into effect was because there had been a number of students in this school in whom tuberculosis had been found.

7: Three schools have given BCG to the students who had a negative tuberculin reaction. This procedure had been discontinued in two of the schools, primarily because the men who are most interested in the work have entered the armed forces.

8: In one of the large cities, one hospital has barred students from tuberculosis wards because a former student contracted tuberculosis and brought suit against the hospital.

In several schools, the students themselves have been interviewed. The Committee has been much pleased with the knowledge the student appears to have regarding tuberculosis. For the most part, students are well informed on the basic concepts of the disease. The Committee also inquired of the students about their use of *Diagnostic Standards* and *X-ray Interpretation of the Chest*. It was discovered that, in each group interviewed, there were one or two students who had a very great fear of tuberculosis.

A great deal of thought has been given to the stimulation of interest in tuberculosis among medical students, and two procedures have been decided upon. One is a post-war project which will be an essay contest on tuberculosis to be conducted in each school. The machinery for this contest has been well thought out and is ready to be put into operation when the medical students get back to normality.

Another method of stimulating the interest of the medical student, which has received the approval of the Committee, is a pamphlet which will dramatize tuberculosis and help to dispel some of the fears which the student now has. It is hoped that a pamphlet such as this will sharpen the student's interest so that he will read the chapters on tuberculosis and chest diseases in the various medical text-books.

AMERICAN TRUDEAU SOCIETY

Some Suggested Procedures for the Early Period of Therapeutic Pneumothorax

A Report of the Committee on Therapy

Dr. H. Corwin Hinshaw, *Chairman*

Dr. John N. Hayes
Dr. John C. Jones
Dr. John D. Steele
Dr. Kirby S. Howlett, Jr.
Dr. T. N. Rafferty
Dr. Andre Cournand

The Committee on Therapy of the American Trudeau Society recognizes that many problems related to pneumothorax treatment remain unsolved and that differences of opinion will continue to exist. However, certain principles may be enumerated which appear to be fundamentally sound and are unanimously approved by the members of this Committee. These are offered in the hope of stimulating discussion which may lead to greater standardization of this therapeutic procedure and possible clarification of statistical reports in future publications.

Pneumothorax should be combined with institutional care from induction of collapse until the disease is brought under control and the pneumothorax stabilized. The use of pneumothorax for patients who are ambulatory from the beginning of collapse is a therapeutic makeshift, which may be dictated by economic and public health necessities but does not constitute a safe or adequate method of treatment and should not be confused with the medically ideal procedure.

Adequate roentgenological guidance is essential to successful and safe management of pneumothorax. Thorough familiarity with the periodic roentgenograms of patients and frequent fluoroscopic examinations of patients by the pneumothorax therapeutist are both required. Circumstances which restrict the free use of either roentgenography or fluoroscopy must be recognized as imposing a serious obstacle to satisfactory management of pneumothorax.

Early closed intrapleural pneumonolysis should be used as an integral part of the pneumothorax program. Adequate facilities should be provided to make this procedure available for all patients who have limiting adhesions which require section.

Pneumothorax in the early stages should be regarded as an exploratory measure. The intended therapeutic action of pneumothorax is in part the elimination of positive sputum arising from the collapsed lung and the closure of any demonstrable cavities. If adhesions which cannot safely be severed prevent the procedure from exerting its intended therapeutic action, it should be promptly abandoned and alternative treatment considered. In this way pleural complications will be greatly reduced.

It is recommended that the degree of pulmonary collapse should be no greater than is necessary to control the disease.

Although these conditions are few, strict adherence to them represents the difference between a logical, careful, well-conceived program and one which may be haphazard, inexact and capable of seriously complicating the entire course of tuberculous disease. The Committee believes that informative statistical studies will be possible and the real value of collapse therapy ascertainable only when standards of this nature are generally accepted and applied.

AMERICAN TRUDEAU SOCIETY

Report of the Michigan-Wisconsin-Minnesota Regional Therapy Conference

Dr. John D. Steele, *Chairman*

A regional conference on tuberculosis therapy, sponsored by the Committee on Therapy of the American Trudeau Society, was held at the Four Seasons Club near Pembine, Wisconsin, on Saturday and Sunday, June 3 and 4, 1944. Michigan was represented by ten delegates, Wisconsin by nine and Minnesota by four. Morning, afternoon and evening sessions were held on Saturday; a morning session only on Sunday.

During the morning and afternoon sessions on Saturday, the roentgenograms and records of 70 cases from each state were presented. These presentations were accompanied by little or no discussion at the time, each delegate making notes of the number of any case which he desired to have re-presented later for discussion.

Dr. Charles R. Smith presented 70 consecutive first admissions to the Copper Country Sanatorium, Houghton, Michigan. These cases were admitted between September, 1941 and July, 1943. Charts were distributed giving the significant data on each patient, including initial and recent sputum examinations, therapeutic procedures employed, complications and the present status of the patient.

Dr. C. M. Yoran presented the 70 resident patients of Rocky Knoll Sanatorium, Plymouth, Wisconsin.

Dr. E. Fenger presented the roentgenograms of 70 consecutive patients who had been admitted to Glen Lake Sanatorium, Oak Terrace, Minnesota, since January 1, 1944.

It was agreed that the number of cases presented was satisfactory. It was further agreed that Doctor Smith's method of selecting his cases for presentation was the most satisfactory one used and gave the best picture of his methods of treatment and results; the resident patients presented by Doctor Yoran did not give an adequate picture of his results; the recent admissions presented by Doctor Fenger did not give an adequate picture of either methods of treatment or results. It is recommended that similar future conferences could well adopt Doctor Smith's method of presentation and selection of cases, although it is realized that presentation of a series of consecutive discharged patients might well give an accurate picture of the methods and results of therapy. Presentation of consecutive discharges would not, however, include those cases which are resistant to treatment and which remain in a sanatorium for long periods of time.

Frank, free and friendly discussion followed presentation of the cases. It was agreed that the exchange of ideas which took place on current problems of tuberculosis therapy was extremely valuable to all present and could not have been obtained as satisfactorily in any other way. Disagreement as to indications, choice of therapeutic procedures and evaluation of results was apparent in some instances. On the other hand, the complete agreement expressed concerning the management of many mutual problems was reassuring.

The following were some of the topics discussed with brief impressions of the opinions expressed on each subject:

Detection of tubercle bacilli in pulmonary secretions: There was a wide variance of opinion as to the definition of a negative sputum and in regard to the emphasis that should be placed on various laboratory procedures for the detection of tubercle bacilli. In general, culture of gastric contents is being widely used by the delegates of Wisconsin and Minnesota in diagnosis and evaluation of results. The majority of the Michigan delegates are using culture or guinea pig inoculation of the sputum alone in evaluating results.

It was agreed that the Committee on Therapy of the American Trudeau Society be requested to consider the definition of a "negative" sputum.

Bronchoscopy is in general being widely used by the sanatoria in all three states, even routinely in some instances before major surgery and, in one institution, routinely before pneumothorax. It was agreed that the prognosis of a patient with severe ulcerative tuberculous tracheobronchitis is extremely poor. Not much enthusiasm was expressed concerning local bronchoscopic treatment of these lesions. Thoracoplasty, if feasible, appeared to be the treatment of choice in these cases; pneumothorax, if induced at all, is used with extreme caution.

Phrenic paralysis is most widely used in Michigan, particularly for minimal lesions, in conjunction with pneumothorax and at the time of discontinuation of pneumothorax. A growing tendency was noted to favor a trial of phrenic paralysis in many instances before instituting pneumothorax. This was particularly evident in the cases presented from Wisconsin. Relatively few permanent phrenic paralyses are being performed by any group represented.

Pneumothorax: Indications for pneumothorax varied to some extent. The Wisconsin group appeared to be the most conservative, preferring at least a preliminary period of observation or a trial of phrenic paralysis before inducing a pneumothorax. On the other hand, more primary thoracoplasties without a trial of pneumothorax are being performed in Wisconsin than in the other two states.

It was generally agreed that a pneumothorax should be promptly abandoned if limiting adhesions (which cannot be divided) prevent a clean, satisfactory relaxation of the lung or if persistent fluid is present in the pleural cavity.

Intrapleural pneumonolysis: It was agreed that closed intrapleural pneumonolysis should be performed as soon as sufficient space is present to allow manipulation of the instruments (usually within one month after induction of the pneumothorax). Open intrapleural pneumonolyses have virtually been abandoned by all present.

Thoracoplasty: The surgical mortality of thoracoplasty as reported by the delegates present does not exceed 2 per cent. Relatively few ribs are resected per stage, rarely exceeding three and tending in general to be less than three. Transverse processes are resected by most surgeons in Michigan and Wisconsin. It was not felt that resection of transverse processes contributed appreciably to the production of scoliosis. Some form of compression device is being used following thoracoplasty in all three states. A tendency was noted in some

cases to decrease the interval between stages to less than three weeks. Local anaesthesia is generally used in Minnesota; general anaesthesia in the larger clinics in Michigan and Wisconsin. Extrapleural gauze packing for uncontrolled lesions following thoracoplasty was recommended by the Minnesota group and some of the Wisconsin group. In general, it was agreed that revision thoracoplasty is seldom necessary or effective if the initial operation has been properly performed.

Miscellaneous: Some form of *cavity drainage* is being used in the treatment of tension cavities either before, during or after thoracoplasty. Preliminary anterior thoracoplasty stages are favored in preparation for cavernostomy prior to posterior thoracoplasty. Residual tension cavities following thoracoplasty were considered to respond well to cavernostomy. Open cavernostomy was definitely preferred to the Monaldi procedure by most of the surgeons present.

Extrapleural pneumothorax is rarely used in Michigan and Wisconsin; it is used more frequently in Minnesota.

Paraffin filling following an extrapleural pneumonolysis is used occasionally, with satisfactory results and practically without complications, in Michigan and Wisconsin; it is no longer used in Minnesota. It was emphasized that this operation should not be used for other than relatively small apical lesions and in no instance should more than 300 grams of paraffin be inserted. The tendency in Wisconsin is to use 200 grams or less. It was also pointed out that the term "pack" which is often used in connection with this procedure is an unfortunate one. The paraffin should not actually be forced into the extrapleural space under pressure but rather laid in the space gently in order to retain the relaxation of the lung produced by the pneumonolysis.

Oleothorax is not widely used, and its use is probably decreasing rather than increasing in the three states represented. It was emphasized that the danger of rupture of the oil into the lung is a very real one and that all patients should be checked (pressures and X-ray films) at not longer than three-month intervals.

Pulmonary resection for tuberculosis had not been used sufficiently by any of the delegates present to warrant discussion of the present status of this procedure in phthisiotherapy, although its use is being considered particularly for certain cases with tuberculous bronchitis.

At the conclusion of the conference, it was unanimously agreed that the conference had been extremely valuable and that similar regional conferences could be highly recommended to other sections of the country. It was also recommended that this same group should reconvene in two years in order to determine whether the discussions at this year's conference had produced any changes in trends of therapy in the interval.

Acknowledgment

An eight panel view box used at the conference was furnished through the courtesy of the General Electric X-ray Corporation.

ANNOUNCEMENT

Sixth Pan American Congress of Tuberculosis

The Organization Committee of the Sixth Pan American Congress of Tuberculosis announces that its meeting will be held in Havana, Cuba, from January 15 to 21, 1945. It is hoped that many members of the Latin American Union of Tuberculosis Societies (U.L.A.S.T.) will be able to attend, as well as some of their North American colleagues.

The three principal topics for discussion will be as follows:

1: Status of BCG in the prevention of tuberculosis.
2: The forms and types of the initial clinical lesions of tuberculosis.
3: Methods of treatment of cavities.

The delegates participating in this Congress will consist of two classes:
Official members—Ex-presidents, committee members and chairmen.
Other members—All physicians who will register paying the fee of three Cuban pesos or three dollars. These physicians will have the right to participate in the scientific discussions, present papers relating to the topics decided upon and to receive the souvenir booklet of the Congress.

The program and by-laws of the Congress will soon be available. Registration should not be delayed, since the Committee would like to know approximately how many plan to submit papers, to attend the Congress, or both.

Any inquiry related to the meeting, hotel rates, travel rates, etc., should be directed, at the earliest possible moment, to the President of the U.L.A.S.T. and the Sixth Pan American Congress of Tuberculosis, Dr. Juan J. Castillo, Linea y N. Vedado, Havana, Cuba.

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